COGNITION IN MOOD DISORDERS

EDITED BY: Allan H. Young and Catherine Harmer
PUBLISHED IN: Frontiers in Psychiatry

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88963-666-2
DOI 10.3389/978-2-88963-666-2

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: researchtopics@frontiersin.org

COGNITION IN MOOD DISORDERS

Topic Editors:
Allan H. Young, King's College London, United Kingdom
Catherine Harmer, Warneford Hospital, United Kingdom

International Society for Affective Disorders (ISAD) exists to promote research into the mood (affective) disorders through all relevant scientific disciplines, including genetics, neuroscience and the social and behavioural sciences. Inter-disciplinary research approaches are particularly highly valued by the society.
www.isad.org.uk

Citation: Young, A. H., Harmer, C., eds. (2020). Cognition in Mood Disorders. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88963-666-2

Table of Contents

frontiers in Psychiatry

EDITORIAL
published: 31 January 2020
doi: 10.3389/fpsyt.2019.01013

Editorial: Cognition in Mood Disorders

Mayowa Oyesanya[1,2], *Catherine J. Harmer*[1,2*] *and Allan H. Young*[3]

[1] *Department of Psychopharmacology and Emotional Research, Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, United Kingdom,* [2] *Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom,* [3] *Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London & South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, United Kingdom*

Keywords: cognition, depression, mood disorders, cognitive biomarker, anxiety

Editorial on the Research Topic

Cognition in Mood Disorders

INTRODUCTION

Mood disorders are common, complex, and one of the main causes of morbidity worldwide (1). There has been an increasing recognition that cognitive dysfunction is a central aspect of most mood disorders, as well as being closely related to the functional impairment that these disorders commonly cause (2, 3). Therefore, appropriate assessment and management of cognitive impairment(s) in mood disorders is important for the optimal treatment of these disorders more broadly. Research in these areas is ongoing and has the potential to improve our understanding of the neurobiological and neuropsychological mechanisms underpinning cognitive dysfunction in affective illness. In addition, developing tools to measure cognitive deficits more objectively, may augment the diagnosis of affective disorder and support current, and future efforts, to improve the classification of psychological symptoms and processes in psychiatry (4). This could allow for the identification of patterns of cognitive deficits which may be more amenable to certain treatments or may be of prognostic utility.

In this editorial, we seek to summarize and organize the research literature published in this special Research Topic — Cognition in Mood Disorders. In this special edition, research papers published within this topic will be discussed within the following headings: the neurobiology of cognition, experimental models for understanding cognition, potential predictive cognitive markers, and the assessment and management of cognitive dysfunction, in mood disorders.

NEUROBIOLOGY OF COGNITIVE DYSFUNCTION IN MOOD DISORDER

This special issue includes a focus on the neurobiological underpinnings of cognitive impairment in different mood disorders. King et al. explored the relationship between neuroinflammatory processes, dysfunction in glutamate neurotransmission, and subsequent cognitive deficits in depression (with a focus on learning and memory). Magnetic resonance spectroscopy of the anterior cingulate cortices of a group of patients with bipolar II disorder and healthy controls, found no difference in anterior cingulate glutamate or inflammatory markers; although poor performance

OPEN ACCESS

Edited by:
Julian Macoveanu, Copenhagen University Hospital, Denmark

Reviewed by:
Philip B. Mitchell, University of New South Wales, Australia

***Correspondence:**
Catherine J. Harmer
catherine.harmer@psych.ox.ac.uk

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *22 October 2019*
Accepted: *20 December 2019*
Published: *31 January 2020*

Citation:
Oyesanya M, Harmer CJ and Young AH (2020) Editorial: Cognition in Mood Disorders. Front. Psychiatry 10:1013. doi: 10.3389/fpsyt.2019.01013

on one of the cognitive tasks, was predictive of a poorer response to psychological therapy. The study was a pilot and generated key hypotheses for future higher-powered studies.

Gao et al. investigated differences in the functioning of the default mode and executive control networks in depressed patients versus a group of controls, using resting state functional magnetic resonance imaging (rs-MRI). A treatment naïve group was chosen to eliminate any potential confounding effect of antidepressant use on neural response. These depressed participants were found to have lower and higher network homogeneity (NH) in different parts of the default mode network. They were also found to have reduced executive function compared to controls. These finding suggest that changes in executive function and the default mode network occur independently of treatment effects in depression.

Wang et al. used transcranial doppler and 320 slice- computed tomography (CT) scanning to measure regional cerebral blood flow velocity and regional cerebral blood flow respectively, in manic patients compared to a group of patients with major depression and healthy volunteers. The authors explain that although such whole brain perfusion scanning using CT has seen use in cerebrovascular disease, its use in psychiatry is relatively novel. Regional cerebral blood flow and velocity was increased in the left medial temporal lobe and the right hippocampus in manic patients compared to the other groups. As the authors state, it would have been of additional interest to have a bipolar depression group as a comparison group in their study. Advances in neuroimaging, as shown in Wang et al.'s study and the others in this issue, have allowed for more rigorous and quantitative assessment of previously uncharted areas of cognition in psychiatry.

Neuropsychological Experimental Models for Understanding Cognition

The studies summarised in this section have used neuropsychological experiments involving healthy participants and/or participants with affective illnesses to analyse specific aspects of cognition of relevance to affective disorders.

Walsh et al. and Chase et al. studied reward processing in healthy volunteers and in bipolar disorder respectively. In Walsh et al.'s study, the administration of a single dose of bupropion (a noradrenaline and dopamine reuptake inhibitor) led to statistically significant differences in emotional processing, but not reward processing, compared to placebo. Using a cued reinforcement reaction time task, Chase et al. found all groups (depressed bipolar, euthymic bipolar, unipolar depression and healthy controls), showed similar reaction time performance in the task, although the euthymic bipolar group showed an increase in commission error rate in high reward conditions. The results of the study provided some evidence for response-calibration deficits that were specific to patients with bipolar disorder.

The other three studies in this section sought to explore the relationship between depressive symptom burden and metacognition (Payne et al.), cognitive control of emotional conflict in clinical versus varying degrees of trait anxiety (Yu et al.) and the association between social cognition and paranoia (Savulich et al.). Payne et al. provide evidence of an association between increasing depressive symptom burden, a greater tendency to adjust levels of confidence in response to new evidence, and lower overall confidence levels. They point to the need in their study to replicate their findings with a sample of patients with clinical depression. Yu et al. demonstrated that deficits in cognitive control of emotional conflict were present in individuals with high trait anxiety, with more severe deficits occurring in generalised anxiety disorder. They hypothesized that trait anxiety may produce these impairments, potentially leading to clinically significant levels of anxiety. Savulich et al. showed that paranoid thinking may reduce cooperation in the pursuit of mutual reward and that delusional ideations can predict maladaptive feelings of shame when experiencing interpersonal harm in a moral emotional processing task.

As these studies have shown, experimental neuropsychological experimental models are important in forming and testing hypotheses about relationships between cognition and other symptom domains that may mediate the relationship between mood disorder and subsequent cognitive impairment.

Potential Predictive and Diagnostic Cognitive Markers in Mood Disorders

Two further articles review the literature to assess the potential of cognitive deficits as predictors of treatment response in depression (Groves et al.) or as intermediate diagnostic phenotypes in bipolar disorder (Kessing and Miskowiak). Evidence from the review by Groves et al. is mixed. Some studies in the review demonstrated an association between poorer baseline cognitive functioning (particularly in executive function and attention) and poorer treatment response, although other studies failed to find this, and this association was also affected by the treatment used (different antidepressants, antidepressant and psychotherapy etc). Due to the methodological heterogeneity of studies included in the Groves et al. review, a qualitative synthesis of these studies was performed. Kessing and Miskowiak concluded there was not enough evidence that cognitive deficits in bipolar disorder were sufficiently specific to the disorder, to serve as useful intermediate diagnostic phenotypes. Therefore, more research is needed to see if cognitive impairments specific to bipolar disorder can be identified.

Smirnova et al. presented interesting data which suggests that linguistic analysis of information produced by healthy participants or participants with mild depression and "normal sadness", can distinguish between these three groups. Participants with mild depression tended to produce longer responses, with their written responses presented more in a narrative than analytical manner compared to healthy controls. Participants with mild depression also tended to use more colloquialisms, tautologies and single clause sentences compared to healthy controls.

Using a prospective study design over a period of 2.5 years, Ruhe et al. investigated whether specific biases in emotional processing, remained in patients with remitted recurrent depression, and whether these deficits could predict illness recurrence. They found that compared to the study control group, such patients had persisting negative attentional biases toward faces and self-relevant characteristics with a negative valence, and tended to misclassify neutral faces as expressing anger or disgust. These differences were not predictive of future depressive recurrence.

Assessment and Treatment of Cognitive Dysfunction in Mood Disorders

The final section of this article outlines the articles which may be the closest to direct clinical translation, as they concern the evidence for the assessment and management of cognitive dysfunction in depression (Zuckerman et al.; Fiorillo et al.), schizoaffective disorder (Lopez-Fernandez et al.) and a trial protocol comparing personalised vs standard therapy for the treatment of cognitive dysfunction in depression (Knight et al.)

Zuckerman et al. emphasize the lack of any gold standard test of cognitive impairment in major depression and the unsuitability of current assessment measures to measure it (e.g., Hamilton-Depression Rating Scale). The use of cognitive behavioural therapy, cognitive remediation therapy, pharmacotherapy and neurostimulation techniques (e.g., transcranial magnetic stimulation), were also outlined in this review. On the other hand, Fiorillo et al. focus on the available validated tools for assessing objective and subjective cognitive dysfunction major depression, such as the Screen for Cognitive Impairment in Psychiatry-Depression (SCIP-D – a measures objective cognitive dysfunction) and the Cognitive complaints in Bipolar Disorder Rating Assessment ("COBRA" – a measure of subjective aspects of cognitive dysfunction) (5).They also outline the need to move towards achieving full recovery of function as the main therapeutic target in major depression, rather than just clinical remission.

Lopez-Fernandez et al. performed a systematic review on the effectiveness of cognitive remediation therapies in schizoaffective disorder, finding some evidence that they can be effective in improving social cognition and neurocognition. These conclusions were however limited by the relatively small of studies available for review and their design limitations.

Knight et al's. proposed clinical trial will finish recruiting patients in 2019 and aims to compare a personalised therapeutic regime targeting cognitive impairment, social cognition, and emotional processing problems, to standard treatment for each of these domains. The personalized therapy will be more tailored and intensive; i.e., a greater number of sessions will be assigned to areas of cognitive dysfunction which were more marked at baseline assessment.

CONCLUSION

The research presented in this issue reflects the diversity and depth of the research into cognition in mood disorders. The exciting articles in this Research Topic give a real insight into the various methodological approaches being used in this research area to illuminate mechanisms, treatment targets, and clinical translation of work in the area of cognition in mood disorders. For example, one promising area of translation is the use of cognitive test batteries to predict treatment in identifying earlier treatment response to depression, and work on this is ongoing (6). Other future areas could include the integration of cognitive markers into systems of diagnostic classification (such as future revisions of the DSM-V and ICD-11), or to develop personalised treatment regimes, developed to effectively address specific cognitive deficits. The current articles provide a fantastic primer in an area whose significance is increasingly evident, and which is developing in new and exciting directions.

AUTHOR CONTRIBUTIONS

MO wrote the first draft of the manuscript. MO, CH, and AY contributed to manuscript revision, read and approved the submitted version.

ACKNOWLEDGMENTS

MO is supported by the National Institute for Health Research (NIHR) and the Oxford Health NHS Foundation Trust. CH is supported by the Oxford Health NIHR Biomedical Research Centre. Prof AY's research is funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

REFERENCES

1. World Health Organisation. (2017). Depression and Other Common Mental Disorders: Global Health Estimates. Geneva. Available at: http://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf;jsessionid=966998E749B1B4A9F9577BF930FCE996?sequence=1.
2. Trivedi MH, Morris DW, Wisniewski SR, Lesser I, Nierenberg AA, Daly E, et al. Increase in work productivity of depressed individuals with improvement in depressive symptom severity. *Am J Psychiatry* (2013) 170(6):633–41. doi: 10.1176/appi.ajp.2012.12020250
3. Lam RW, Kennedy SH, McIntyre RS, Khullar A, et al. Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. *Can J Psychiatry* (2014) 59(12):649–54. doi: 10.1177/070674371405901206
4. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry. U S* (2014) 171(4):395–7. doi: 10.1176/appi.ajp.2014.14020138
5. Ott CV, Bjertrup AJ, Jensen JH, Ullum H, Sjælland R, Purdon SE, et al. Screening for cognitive dysfunction in unipolar depression: validation and evaluation of objective and subjective tools. *J Affect Disord* (2016) 190:607–15. doi: 10.1016/j.jad.2015.10.059
6. Kingslake J, Dias R, Dawson GR, Simon J, Goodwin GM, Harmer CJ, et al. The effects of using the PReDicT Test to guide the antidepressant treatment of depressed patients: study protocol for a randomised controlled trial. *Trials. BioMed Central* (2017) 18(1):558. doi: 10.1186/s13063-017-2247-2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past collaboration with one of the authors MO.

frontiers in Psychiatry

CLINICAL STUDY PROTOCOL
published: 12 December 2017
doi: 10.3389/fpsyt.2017.00280

Psychosocial Dysfunction in Major Depressive Disorder—Rationale, Design, and Characteristics of the Cognitive and Emotional Recovery Training Program for Depression (CERT-D)

*Matthew James Knight and Bernhard T. Baune**

Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Mario F. Juruena,
King's College London School of Medicine, United Kingdom
Taolin Chen,
West China Hospital of Sichuan University, China

***Correspondence:**
Bernhard T. Baune
bernhard.baune@adelaide.edu.au

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *14 September 2017*
Accepted: *29 November 2017*
Published: *12 December 2017*

Citation:
Knight MJ and Baune BT (2017) Psychosocial Dysfunction in Major Depressive Disorder—Rationale, Design, and Characteristics of the Cognitive and Emotional Recovery Training Program for Depression (CERT-D). Front. Psychiatry 8:280. doi: 10.3389/fpsyt.2017.00280

Introduction: Psychosocial dysfunction is associated with poor longitudinal course of depression and is not sufficiently addressed by existing pharmaceutical or psychological treatments. The aim of the current study is to evaluate the efficacy of a novel intervention designed to improve psychosocial function in depressed individuals. Impaired cognition, emotion processing, and social cognition appear to underlie (i.e., cause) psychosocial dysfunction in depression. The current treatment will target functioning in these domains (i.e., cognition, emotion, social cognition) with repeated training tasks, following the rationale that therapeutic benefits will arise in psychosocial functioning. It is expected that personalizing treatment by participants' baseline functioning will enhance clinical efficacy, by comparison with standard treatment in which baseline functioning is not considered.

Methods: The study is a randomized, controlled treatment (RCT), in which the efficacy of a personalized and standard intervention will be compared. Sixteen treatment sessions will be administered over an 8-week period. These treatments are designed to improve cognition, emotion processing and social cognition. Assessments of psychosocial functioning, as well as a number of secondary outcomes, will occur at baseline, 4 weeks (mid-RCT), 8 weeks (end of RCT), and in the observational period at baseline (week 9) and 3 and 6 months post-RCT. Recruitment will commence in July 2017, including subjects diagnosed with major depressive disorder according to DSM-IV-TR criteria.

Discussion: This research will provide new insight into the roles of cognition, emotion processing, and social cognition in psychosocial dysfunction in depression. In addition, the relative clinical efficacy of personalized versus standard treatment approaches will be assessed.

Ethics and dissemination: This study has been approved by the human research ethics committees of the Royal Adelaide Hospital and the University of Adelaide (ethics code: R20170611). The study has been registered with the Australia and New Zealand

Clinical Trials Registry Registration number: ACTRN12617000899347, web link: http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617000899347p. The results of the current study will be published in academic journals following completion of recruitment in 2019. Data will be owned and retained by the University of Adelaide, with access restricted to the research team responsible for the study.

Keywords: depression, cognitive training, cognitive remediation, psychosocial functioning, social cognition, emotion processing

INTRODUCTION

Depression is the leading cause of mental illness worldwide, affecting approximately 322 million individuals (1). The illness is characterized by prolonged negative mood, anhedonia, and impaired cognition. Depressed individuals also demonstrate significantly impaired psychosocial function, indicated by diminished organizational, occupational, and social ability (2, 3). In addition to the substantial burden of depression on the daily lives of individuals (4) depression impacts on a societal level by reducing occupational productivity (5, 6). Established therapies (e.g., psychotherapy, CBT) and pharmaceutical treatments are costly and lead to high rates of recurrence in the long term (6). As a consequence, there is a clear need to develop alternative and/or complimentary treatments for depression.

It is possible that existing treatments for depression underperform because they do not sufficiently address psychosocial functioning (2, 7). Psychosocial function can be defined on a micro level as our day-to-day ability to contend with environmental and social tasks (e.g., maintaining work and relationships), and on a macro level as the pursuit of significant life outcomes (e.g., self-actualization) (7). Previous work has operationalized these dimensions, such that quantitative and psychometrically valid assessments of psychosocial impairment have been established (7–9). Psychosocial functioning appears to be related to a number of other functional outcomes (e.g., positive future outlook, ability to derive pleasure from life events), suggesting that psychosocial function contributes to mental health in general (10, 11). Psychosocial dysfunction is prevalent in depressed individuals and does not appear to improve even in patients who are symptomatically recovered (3). Ongoing psychosocial dysfunction may lead to recurrent episodes of depression, as impaired functioning negatively interacts with cognitive and emotional vulnerability in previously depressed individuals (2, 12–14).

Existing evidence indicates that cognitive, emotional, and social cognitive factors underlie deficits in psychosocial functioning (11, 13–16). The proposed study follows this model, stipulating that improvements in cognition, emotion, and social cognition should flow on to psychosocial functioning. Given the importance of this model in the current study, the relationship between the three underlying domains and psychosocial functioning will be explored.

Cognitive Impairment

According to DSM-5 criteria the cognitive symptoms of major depressive disorder (MDD) are impaired decision making, management of attention, and coordination and maintenance of information in working memory (17). Research has also identified deficits in verbal ability (18), visuospatial processing (19), and psychomotor speed (19). The finding that cognitive deficits occur across multiple domains suggests that depression interferes with underlying cognitive faculties, and with the coordination of cognitive subsystems, rather than interfering a specific modality of cognition. Our cognitive abilities are crucial to daily functioning, and to the severity of several cognitive difficulties associated with depression (e.g., hyper-sensitivity to negative feedback). Cognitive treatments target improvement of cold cognition, with the rationale that increasing functioning will benefit performance in hot cognitive tasks, and hence improve experience of everyday life, psychosocial functioning, and day-to-day functioning. In addition, cognitive impairments may mutually interact with emotional and social factors to maintain or exacerbate depression, or lead to recurrent episodes (14, 16).

Psychosocial and cognitive impairments in depression and in other illnesses are associated with elevated levels of several inflammatory cytokines (20, 21). Research by the Baune group (22, 23) demonstrated that IL-8, IL-1beta, and tumor necrosis factor (TNF) are associated with memory, processing speed and motor function in the elderly. In addition, inflammatory C-reactive protein (CRP) may also be associated with depression symptoms (24), and the neurotransmitters 5HT, DA, and NE appear to be related to psychological stress (25). Investigating biomarkers for psychosocial functioning and cognitive dysfunction presents a valuable area for research, as there is potential for developing objective measurements of dysfunction predisposition, for improving our understanding of the neurological mechanisms of depression and associated poor psychosocial functioning (e.g., neurotrophic theory), and for improving pharmacological treatments that address not only symptoms of depression but also psychosocial functioning and workplace functioning.

A large body of work has investigated the selective treatment of impaired cognition in depression with cognitive remediation programs (2, 5, 26), which typically involve repeated completion of cognitive tasks over several weeks. The results of such programs generally reveal that patients improve on measures of executive, visuospatial, and verbal function (2). These results support the theory that repeated activation of brain regions *via* cognitive treatment increases neuroplasticity and improves neural function (27). Although cognitive gains following remediation programs are relatively consistent, the transfer of this benefit to occupational function, resilience, and psychosocial functioning are not well established (15). It is possible that transfer of cognitive skills does not reliably occur because remediation programs do not also address impaired

social cognitive skills and emotional processing, which may negatively interact with cognition on depression outcomes. The following paragraphs discuss the role of emotion processing and social cognition in MDD, and highlight how an integrated and personalized treatment approach may be critical to maximizing treatment outcomes.

Emotion Processing

Our experience of emotion is fundamentally linked to cognition. Evidence for this link is demonstrated at a neurological level by overlap in activation patterns of cognitive processes and emotional experience (28–30). The phenomenological parallels of emotion and cognition are consistent with cognitive models of depression (31), which stipulate that interplay between cognitive vulnerability and negative emotion both lead to and sustain MDD. Specifically, cognitive models stipulate that attention and memory systems are biased to focus on negative information, suppress adaptive coping strategies (e.g., flexibility), and encourage maladaptive strategies (e.g., rumination) (32). The critical importance of emotion processing in coping and information processing supports the importance of this factor in determining overall psychosocial functioning (15).

The close overlap between emotion and cognition suggests that cognitive remediation should not neglect the role of emotion in treatment programs (33). Previous work in cognitive–emotional treatment has shown promising results in the implementation of working memory tasks with valenced stimuli (34, 35). Iacoviello et al. (35) conducted a study comparing the benefit of an integrated cognitive–emotional treatment task with that of a pure cold cognitive treatment task for subjects with MDD. The results showed that the integrated cognitive-emotional training resulted in greater reduction in depression symptoms and negative self-referential biases. By contrast, both the cold cognition and integrated tasks resulted in similar gains in attention and working memory performance. These findings are consistent with the notion that cognition and emotion are closely linked, and imply that an integrated treatment approach may result in broader transfer of therapeutic benefit.

Recent work by Wu et al. (36) suggests that dysfunctional emotion processing may play a crucial role in the development and maintenance of geriatric depression. The authors evaluated the positive effect of reminiscence therapy, in which older female patients with depression symptoms verbally recounted earlier life experiences by viewing pictures of past events. A clinical nurse encouraged the patient to recount these memories from different perspectives, and highlighted positive comparisons with the patients' current lives. Posttreatment anxiety and depression symptoms were reduced, suggesting that encouraging flexible and positive retrieval of episodic memory may attenuate negative emotion processing. It is possible that emotional dysregulation may play a greater role in geriatric depression than in standard MDD, as the elderly often lack sufficient social support and experience rapid physiological decline (36). Taken together, these findings suggest that older subjects in the current treatment may benefit from emotion processing training tasks focused on redressing negative social biases and negative self-evaluations.

Social Cognition

Social cognition refers to the perception, identification, and interpretation of social information in interpersonal interaction (16). Maintaining function in this domain involves incorporating information from a range of social cues including prosody, facial expression, body language, verbal content, and theory of mind. Research has identified that social cognition may be impaired in individuals with depression, though the social cognitive deficit is less severe than in other psychiatric illnesses (e.g., schizophrenia) (37, 38). However, social cognition deficits in depression should not be overlooked, as issues with social interaction are associated with suicidality (39), and with severity of depression symptoms (40, 41).

Given the complexity of social interactions, it stands to reason that cognitive functions (e.g., attention, processing speed) are crucial in maintaining fluid and adaptive social ability. Likewise, emotional recognition and bias play an important role in identification and perception of social information. Impaired emotion recognition may cause incorrect or biased assessment of social interaction, which may exacerbate depressed mood and lead to further negative social interactions (16). In turn, negative social experiences may lead to subsequent avoidance of interpersonal interactions, further enhancing feelings of isolation and impaired mood. The interplay between social cognition, emotion, and general cognition further highlights the need for an integrated treatment approach. In addition, the broad and inter-related deficits associated with social cognitive issues suggest this factor contributes substantially to psychosocial functioning. This being said, the link between social cognition and psychosocial functioning has only recently been empirically investigated (16), and pilot data from our group suggest this relationship; supporting the need for the current research.

Social cognition is typically evaluated by one's ability to read facial emotions (42). Depressed persons are typically impaired in facial affect recognition, in part due to a tendency to negatively interpret facial emotions (43). A plausible explanation is that impaired attention and emotional interpretation may cause depressed individuals to focus on mood-congruent (i.e., negative) features of facial affect. Other studies of social cognition employ videos of social interactions, which are intended to be more naturalistic and contain more dynamic social features (i.e., body language, prosody, verbal information) (44, 45). These tasks emphasize theory of mind, as reliance on syntactic and visual information alone is insufficient to detect nuanced social interactions (e.g., sarcasm). Social cognition can also be measured with prosody tasks, in which several syntactically identical sentences are presented with different emotional intonations.

The current treatment will use an integrated approach in which cognitive remediation and cognitive training techniques are employed with cognitive, emotional, and social cognitive stimuli. While traditional cognitive training has been shown to increase psychosocial functioning (46, 47), it is expected that the addition of emotional and social training domains will extend and enhance this effect. Similar techniques have been employed to address emotional and social impairment in other psychiatric illnesses, including bipolar (48) and schizophrenia (49). The

results of these studies suggest that social and emotional training may provide benefits in domains of daily life (e.g., occupational functioning). The clinical efficacy of these strategies in treating major depression has not yet been evaluated and is hence a primary interest of the current study. It is expected conducting remediation and training in three domains (i.e., cognition, emotion processing, and social cognition) will improve psychosocial functioning to greater extent than is achieved by treating cognition alone.

Personalization

Given the multifaceted nature of impairment in depression, it is reasonable to assume that deficits will not occur in a uniform nature within individuals. Certain individuals may be disadvantaged specifically in domains of emotional processing, while others are more disadvantaged in terms of cold cognitive ability or social cognition. Previous interventions may not have led to consistent improvements in psychosocial functioning because individual differences in domain-specific impairment were not addressed. In fact, existing interventions assume that group means (i.e., norms) reflect impairment at an individual level, and hence that a generalized treatment approach is sufficient. Given the heterogeneity of impairment observed between individuals with MDD (12), it is possible that a standard treatment approach is not optimal (50). In particular, standard treatment approaches may misappropriate resources and time to clinical domains which are not relevant or helpful to the individual. In contrast, personalized approaches tailor treatment by targeting baseline deficits within individuals, enabling treatment to focus on impaired domains, while also spending less time addressing more functional domains. Personalization may improve treatment efficiency and efficacy, in contrast to the traditional standard approach.

The current investigation will evaluate the personalized approach, by comparing psychosocial functioning following a personalized intervention and a standard (i.e., non-personalized) intervention. The personalized intervention will tailor treatment tasks around baseline individual deficits, such that the individual's most impaired domains receive the greatest attention. Given the importance of cognition, emotion processing, and social cognition in determining psychosocial functioning, the CERT-D treatment will be tailored by patterns of impairment observed in these three domains. For example, a participant who demonstrates severe cognitive impairment will receive a greater number of treatment sessions devoted to cognition, with fewer sessions devoted to emotion processing and social cognition. Overall, it expected that both personalized and standard treatments will result in improved psychosocial functioning, which is expected to be retained over a 6-month observational period. However, it is predicted that the clinical effect on psychosocial function will be greater following personalized, relative to standard, treatment.

In summary, the cognitive and emotional recovery training program for depression (CERT-D) study will evaluate a novel treatment for depression, employing an integrated cognitive, emotional and social cognitive approach. The primary outcome will be change in psychosocial function over the intervention and subsequent observational period. Performance in several secondary domains will also be evaluated, including depression symptom severity, resilience, occupational functioning, cognitive failures, and functional disability. In addition, the study will examine biomarkers of cognitive and psychosocial dysfunction in depression, providing an opportunity to expand our knowledge of this domain. This research will advance the field by evaluating the efficacy of integrating training of cold cognition with emotion processing and social cognition. The integrated approach contrasts with traditional cognitive remediation, which has primarily focused on the improvement and application of executive training. In addition, the current methods allow evaluation of the relative clinical efficacy of personalized and standard treatment approaches in remediating psychosocial dysfunction in MDD.

METHODS

Objectives

The primary objective of the CERT-D is to evaluate whether treating cognition, emotion processing, and social cognition leads to immediate and longitudinal benefit in psychosocial functioning. To achieve this objective, participants will complete either a personalized or standard (non-personalized) treatment devoted to increasing performance in these domains. Participants in the personalized group will receive a tailored treatment incorporating a greater number of sessions devoted to their domain(s) of primary baseline dysfunction. By contrast, the standard treatment group will complete a pre-established battery of treatment independent of baseline deficits.

The key hypotheses and aims of the current study are as follows:

Hypothesis 1: Overall, psychosocial functioning will be improved at 8 weeks [end of randomized, controlled treatment (RCT)] relative to baseline. Psychosocial functioning in the observational period (post-RCT) will not decline at 3 and 6 months relative to post-RCT baseline.

Related Aim: To evaluate which subdomains of psychosocial function (e.g., autonomy, social relationships) are sensitive to change over time from the CERT-D.

Hypothesis 2: Performance in secondary outcome measures will improve at 8 weeks relative to baseline, and will be retained over a 6-month observational period. Secondary outcomes include occupational functioning, cognitive failures, functional disability, resilience, and depression symptom severity.

Hypothesis 3: It is expected that the personalized treatment group will display greater psychosocial improvement at 8 weeks (compared to baseline) than subjects who complete a standard treatment.

Hypothesis 4: Biological and genomic signatures will be associated with psychosocial functioning, as well as cognitive, emotional, and social cognitive performance.

Study Design and Recruitment

The CERT-D study will commence in July 2017. The study will be a RCT, comparing the clinical efficacy of a personalized and standard intervention. Psychosocial functioning is considered the primary outcome. An effect size of approximately $d = 0.5$ is expected with regards to change in psychosocial function over the intervention. Given the intended sample size of 100, the study will achieve statistical power of 89% ($1 - \beta = 89$). The rationale for this "medium" effect size is that previous interventions have found positive outcomes approximate to this magnitude (5, 35), for example in cognitive functioning.

The trial will include 16 treatment sessions designed to improve cognition, emotion processing, and social cognition administered over an 8-week period. Assessments will occur at baseline, 4 weeks (mid-RCT), 8 weeks (end of RCT), and in the observational period at baseline (week 9) and 3 and 6 months post-RCT (see **Figure 1**). Assessments will measure psychosocial functioning, cognition, emotional state, social cognition, as well as occupational functioning, depression symptom severity, functional disability, cognitive failures, and resilience. Three assessment visits will also include taking blood for biomarker and genetic analysis. Recruitment will include individuals between the ages of 18 and 75, who will be invited to participate *via* research clinics of the Department of Psychiatry, University of Adelaide, and within the Central Health Network in Adelaide, South Australia. It could be argued that the age range should be restricted to younger adults (<60), such that subjects with geriatric depression are excluded. However, recent work has suggested that cognitive training strategies are efficacious in the treatment of geriatric depression (47, 51, 52). Given the current intervention shares many components of traditional cognitive training, it is suggested that the CERT-D intervention should benefit older (i.e., 60–75 years) patients.

Inclusion and Exclusion Criteria

Individuals with mild–moderate MDD according to DSM-IV-TR criteria (17) will be recruited for the current study. Severely depressed subjects will not be included, as the complexity from treatment tasks would likely result high rates of deterrence. Subjects identified through screening with bipolar or anxiety disorders will be excluded, as will subjects with schizophrenia, a learning disorder, eating disorder or a pervasive developmental disorder. Subjects with current brain injury or impairment which could affect cognitive function (e.g., neurodevelopmental disorders, dementia) will be excluded. In addition, subjects will be withdrawn following subsequent severe brain/head injury, development of dementia, psychosis, or development of neurological conditions such as multiple sclerosis or Parkinson's disease.

Ethics

The CERT-D has been approved by the Human Research Ethics Committees at the Royal Adelaide Hospital (approval number: R20170611) and The University of Adelaide (approval number: R20170611). All details of participant involvement will be conveyed to study participants both in writing and verbally before informed consent is obtained.

There are no severe adverse effects expected to result from the current treatment. However, participants will be withdrawn from treatment if they demonstrate a significant increase in depression symptom severity [20% increase in Montgomery Asberg Depression Rating Scale (MADRS) score] and referred to their treating psychiatrist or GP.

Randomization Process

After screening, subjects will be randomly allocated with computer software to receive either personalized or standard (non-personalized) treatment (see **Figure 2**). In both the standard and personalized intervention groups each treatment session will consist of domain-specific tasks. Every treatment session will be repeated at least once, to ensure that subjects have the opportunity to practice the treatment tasks.

Personalized Treatment

Personalized interventions will be tailored to address subjects' most impaired domains. Domain-specific tests will be administered at baseline to determine the modality and degree of individual impairment. On the basis of baseline deficits, subjects in the personalized group will be allocated to one of four potential treatment arms; (1) high cognition treatment, (2) high emotion treatment, (3) high social cognition treatment, and (4) broad

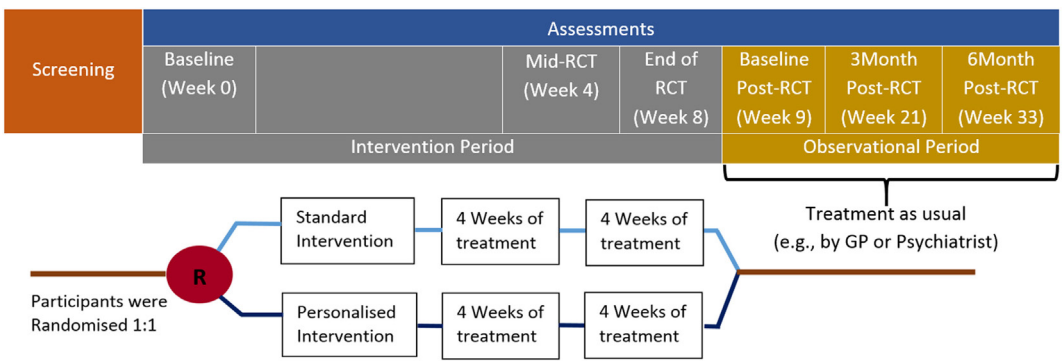

FIGURE 1 | Clinical timeline for the CERT-D. Participants will complete 2 training sessions per week (16 sessions total) over the 8-week intervention period.

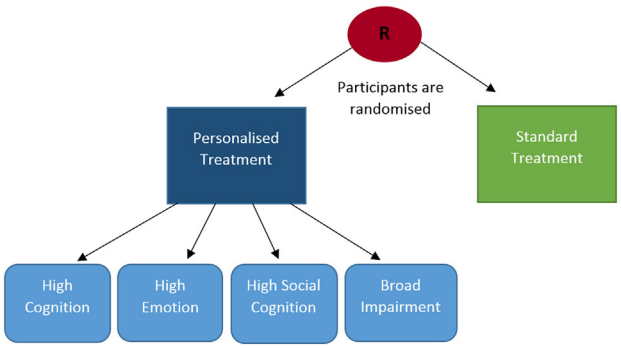

FIGURE 2 | CERT-D randomization process. Several streams of treatment are available for subjects in the personalized group (high cognition, high emotion, high social cognition, broad impairment), whereas treatment is the same for every participant in the standard treatment group.

impairment treatment (see **Figure 2**). Subjects will be allocated to streams 1, 2, or 3 if impairment is primarily represented in one of the three baseline domains. In treatment arms, 1–3 subjects will complete a greater number of intervention sessions devoted to the domain of primary dysfunction. Subjects who are significantly impaired in two or more domains will be allocated to broad impairment treatment. Broad impairment treatments will incorporate a similar number of intervention sessions in each domain, but will be initiated more gradually (i.e., initial treatment sessions will be shorter in duration) and will use simpler tasks.

Standard Treatment

Subjects allocated to the standard (i.e., non-personalized) intervention will receive an identical intervention regardless of baseline impairment. The standard intervention will be comprised of approximately an equal number of treatment sessions in each domain. Unlike broad impairment treatment, standard treatment sessions will be the full duration from the outset and the difficulty curve of treatment tasks will be steeper.

CLINICAL, SELF-REPORT, AND COGNITIVE ASSESSMENTS

Screening

Participants will be screened for presence of MDD with the MINI 600 Neuropsychiatric Diagnostic Interview. The MINI is well validated and has demonstrated high specificity and sensitivity, as well as close concordance with the American Psychiatric Association Diagnostic Criteria (SCID), and the Composite International Diagnostic Interview (ICD-10) (53, 54). The MADRS will also be administered as a measure of depression symptom severity (55).

Assessment Visits (Baseline—6 Months Post-RCT)

In total, six assessments of functioning and performance will occur over the CERT-D timeline (see **Figure 1**). In the intervention period, subjects will complete assessments at baseline, 4 weeks (mid-RCT), and 8 weeks (end of RCT). The observational period will comprise assessments in week 9 (baseline post-RCT), as well as 3 and 6 months post-RCT.

Psychosocial Functioning

Psychosocial functioning will be assessed with the Functioning Assessment Short Test (FAST); a clinician administered 24-item scale. The FAST includes questions which gauge subjects' abilities across several psychosocial domains of daily living (e.g., autonomy, leisure, financial issues). The FAST takes approximately 6 min to complete (9) and will be administered by a clinician blind to experimental group allocation.

Cognitive Functioning

Cognitive functioning will be assessed with the THINC-it tool; a digitally administered screening instrument for cognitive impairment in depression. The THINC-it involves four objective tests of cognitive performance, including choice reaction time, a *1*-back memory task, the Trail Making Test Part B and digit symbol substitution. The THINC-it also includes a 5-item component of the self-reported perceived deficit questionnaire, as an indication of retrospective cognitive dysfunction (56).

Emotion

Participants' emotional state will be assessed with the Positive and Negative Affect Schedule (PANAS), which requires subjects to indicate the intensity of current and recent emotions. Scores are calculated separately for positive and negative emotions, with higher scores indicating greater intensity. The separability of positive and negative mood scores enables discriminate bilateral mood evaluation, which is not possible with unilateral scales or with measures of depression symptom severity alone. The PANAS has well-supported psychometric properties, including high internal consistency and convergent and discriminant validity (57, 58).

Social Cognition

The Weschler Adult Intelligence Scale Advanced Clinical Solutions Social Cognition Test (WAIS-IV-ACS) will be used to assess participants' social cognition. This component of the WAIS was developed in response to the finding that memory for faces and affect recognition was independent of other cognitive abilities, suggesting a unique neuropsychological construct in social cognition (38). The test involves three tasks designed to identify social cognitive impairment: Affect Naming, Prosody-Face Matching, and Prosody-Pair Matching.

Depression Symptom Severity

Depression symptom severity will be assessed with the MADRS and the Structured Interview Guide of the Hamilton Anxiety and Depression Scale (SIGH-AD). The SIGH–AD is a 31-item structured interview that combines the Hamilton Depression Scale (HAM-D, 17 items) and the Hamilton Anxiety Scale (HAM-A, 14 items) (59).

Work Productivity

Two scales will be used to evaluate occupational functioning: The Endicott Work Productivity Scale (EWPS) and the Work

Productivity and Impairment Questionnaire (WPAI). Both the EWPS and WPAI are self-report questionnaires designed to measure occupational productivity (60, 61). Importantly the EWPS measures overall occupational impairment, whereas the WPAI measures the extent to which a particular issue (e.g., depression) negatively affects occupational functioning.

Resilience

Resilience will be assessed with "The Resilience Scale" (62). The scale involves completing a 26-item Likert scale, of which each item makes a broad statement measuring the participants' perceived resilience (e.g., "I usually manage one way or another"). The Resilience Scale has shown high internal consistency and concurrent validity (63), as well as validation with a number of age and ethnic groups (64).

Functional Disability

Disability in daily life will be evaluated with the Sheehan Disability Scale (65, 66). This will involve participants self-reporting the extent to which depression symptoms disrupt three domains: (1) work/school, (2) social life, and (3) family life/home responsibilities. The Sheehan disability scale achieves high internal consistency (0.89) and concurrent validity, with high scores are indicative of mental health disorders (65).

Cognitive Failures

Cognitive failures can be defined as everyday slips of memory and attention (e.g., forgetting a colleague's name). The current study will evaluate cognitive failures with the Cognitive Failures Questionnaire (CFQ), which gages the frequency of cognitive failures experienced in the past 6 months. The CFQ appears to have acceptable construct validity, as factor analysis has indicated that CFQ items load primarily to a single construct (67).

Blood Specimen

Blood taking will occur at baseline, week 8 (end of RCT), and at 6 months post-RCT. These samples will enable analyses of biomarker associations with psychosocial functioning, as well as the effect of the CERT-D intervention on biomarker levels. Blood serum analyses will include of evaluation of cytokine concentration (e.g., IL-8, TNF), CRP levels, and neurotransmitter activity. Samples will be stored in secure refrigerators with stringent access rights at the Adelaide Health and Medical Sciences building.

CERT-D INTERVENTION DETAILS

The intervention is comprised of 16 total treatment sessions. Each session will be devoted to one of the underlying domains of psychosocial functioning targeted by the CERT-D (i.e., cognition, emotion processing, social cognition). Tasks completed within sessions will be presented in both digital and pen and paper formats. Several digital tasks will be completed with the psychology experiment building language (PEBL) software (68), which incorporates a number of freely distributed psychological tests presented in a game-like manner. Other treatment tasks will be administered in a pen and paper format.

Cognition Treatment

Cognition treatment sessions will involve cold cognition tasks, with the expectation that subjects' performance in these tasks will improve over time. The researcher will emphasize the value of cold cognitive skills in everyday life and discuss transfer of these skills to functional domains (e.g., psychosocial functioning). Each cognition session will focus on one of three cognitive modalities: Executive functioning, visuospatial working memory, and verbal working memory (69). Executive treatment sessions will focus on attention, inhibition, problem solving and mental updating (70). Executive tasks include Berg's card sorting test, symbol counting, and the Stroop task (68). Visuospatial treatment sessions will focus on spatial learning, mental rotation, and spatial coordination (71), including map learning (72), figure learning, Corsi blocks (73), and matrix rotation tasks (68). Verbal treatment sessions will target verbal sequencing, reading span, and digit span (74). Verbal training will utilize immediate and delayed verbal memory tasks in the SCIP battery (75), and the reading span and digit span tests in PEBL (68).

Emotion Processing Treatment

The aim of emotion processing sessions will be to address negative emotional biases and cognitive-emotional (i.e., "hot cognition") impairment in depression. Training tasks will attempt to increase participants' performance in hot cognitive tasks, in which depressed patients typically underperform (34). In addition, the subject will be encouraged to discuss any cognitive–emotional issues which arise in these training sessions, which the expectation that raising awareness and understanding may help subjects cope with and overcome emotional dysfunction (e.g., emotional avoidance, poor reappraisal) (32). Emotional treatment tasks include emotional brain storming (49), an emotional *n*-back (35), and emotion word list tasks (76). Taken together, these tasks are intended to embed emotional stimuli within traditional cognitive remediation techniques (e.g., the *n*-back task). These strategies are based on the rationale that improving cognitive management and processing of emotional material will reduce negative attentional and cognitive biases in subjects with MDD (35).

Social Cognition Treatment

Social cognitive training sessions will involve targeting performance in domains of facial affect recognition, prosody detection, body language, and interpersonal communication. Taken together, it is intended that social cognitive treatment will improve subjects' ability to synthesize a broad spectrum of social information, make clearer theory of mind judgments, and reduce social tension and avoidance. The researcher will emphasize the importance of social cognition in everyday life and encourage participants to exercise acquired social skills outside of treatment sessions. Social cognition training tasks will include a "reading the mind in the eyes" task (77), an interpersonal word list task (78) and theory of mind scenarios (44, 45). These tasks are designed to improve the evaluation of facial affect, verbal tone, and body language, while also highlighting the pitfalls of making unfounded or overly negative assumptions about others' intentions and emotions.

INTERVENTION OUTCOMES, ANALYSES, AND DISSEMINATION

The primary outcome of the CERT-D will be psychosocial functioning. Specifically, it is expected that psychosocial functioning will improve at 8 weeks (end of RCT) relative to baseline. Post-RCT psychosocial functioning is expected to be maintained over the 6 months observational period. Performance in secondary outcome measures is expected to demonstrate a similar effect of treatment. Secondary outcomes include depression symptom severity, occupational functioning, resilience, functional disability, and perceived cognitive failures. In addition, the personalized treatment group is expected to show greater improvement over time relative to the standard treatment group. Finally, the association between biomarkers and psychosocial and cognitive performance before and following treatment will be evaluated.

Statistical analyses will be performed with a mixed model ANOVA with time (baseline, 8 weeks, baseline post-RCT, 3 months post-RCT, 6 months post-RCT) and treatment type (personalized, standard) as independent variables. Psychosocial functioning (FAST score) will be the dependent variable. It is expected that overall psychosocial functioning will improve at post-treatment relative to baseline, and that this improvement will be greater in the personalized treatment arm relative to the standard treatment arm. Biomarker analyses require specifically tailored software and will ultimately be entered into simple and stepwise linear regression analyses. These analyses will determine whether individual biomarkers (e.g., CRP), or combinations of biomarkers, are related to cognition (i.e., THINC-it performance) or psychosocial functioning.

Within the personalized treatment group, further analyses will evaluate whether there are any differences in psychosocial functioning owing to the domain-specific treatment groups. That is, will there be any differences in post-RCT psychosocial functioning between the high cognition, high emotion, and high social cognition treatment groups? Given the novelty of the current treatments, these analyses will be exploratory. As with the primary outcome, analyses for this outcome will be conducted with mixed model ANOVAs.

The anonymized data obtained in the current study will be owned by the University of Adelaide, with access restricted to the research team responsible for the project. The results of the CERT-D study will be published in scientific journals, which will discuss clinical efficacy of personalized and standard approaches in light of the data obtained. The authors will also conduct a public lecture to discuss the broader topic of personalized psychiatry, which will include dissemination of outcomes in the current study.

DISCUSSION

Existing literature suggests that psychosocial functioning is associated with depression severity and with longitudinal treatment outcomes (2, 3). Mutual interaction between psychosocial domains (e.g., work productivity, socializing) in depressed persons may exacerbate, maintain, or lead to recurrent depression. As an example, poor cognitive functioning may lead to issues maintaining work, which will cause financial strain and lead to reduced social interactions and impaired affect. Given the importance of psychosocial functioning in depression recovery, the development of treatments designed to target psychosocial functioning is justified.

Current research by the Baune group suggests that cognitive, emotional, and social cognitive domains underpin psychosocial functioning (12, 16). The CERT-D will target these domains with repeated training sessions over an 8-week intervention period. Cognitive and cognitive–emotional treatment approaches for depression have received empirical support (2, 32, 35). Initial research suggests treating social cognition may also be beneficial (16, 79, 80); however, further evidence is needed to establish the efficacy of treating social cognitive functioning in depression. The CERT-D study addresses this gap in knowledge by evaluating a treatment approach integrating all three underlying domains of psychosocial functioning (i.e., cognition, emotion processing, and social cognition). Treatment benefits of the CERT-D are intended to transfer to occupational functioning, resilience, functional abilities, and cognitive performance. Reinforcing improved performance and positive interaction between these domains is expected to develop a framework which encourages and rewards reduction of depression symptoms.

The directionality of recovery in the CERT-D is divergent from traditional depression therapies. That is, existing therapies (e.g., psychotherapy) target reduction in negative depression symptoms with the expectation that improvements in functional and psychosocial domains will follow. By contrast, the current treatment targets psychosocial and functional improvements from the outset. Importantly, the CERT-D integrates treatment across cognitive, emotional, and social domains rather than focusing on one of these domains alone. Integrating treatment across multiple domains is intended to counteract negative feedback between impaired domains which may occur in more selective treatments.

A possible disadvantage of administering training across three domains is that treatment benefits to cold cognitive functioning (e.g., executive functioning) will be attenuated in comparison to traditional cognitive remediation. Reduced executive gains in the CERT-D treatment could result from the equal emphasis given to social, emotional, and cognitive domains, as opposed to focusing purely on cold cognition. However, we do not anticipate this issue to be a crucial issue for two key reasons: (1) emotional and social–cognitive training demand similar cognitive effort and are equally complex in comparison to traditional cognitive training. As a result, emotional and social training may also benefit executive functioning. (2) Individuals who demonstrate significantly impaired cold cognition will be allocated to the "High Cognition" program within the personalized arm. This treatment program emphasizes cognitive treatment above emotional and social domains, and will hence evaluate the efficacy of predominantly cognitive training, relative to training all three domains in the "standard" treatment group. If cognition training alone is identified as having greater clinical efficacy than the integrated training approach, then this finding will also contribute to the value of the current study.

In summary, the CERT-D will make three primary contributions: (1) the evaluation of a novel psychological treatment for

depression. Psychosocial function is considered the primary outcome, and is expected to be improved by integrated treatment of underlying domains. (2) The comparison of the relative clinical efficacy of personalized and standard treatment approaches. Taking baseline deficits into account may enable more efficient and effective psychosocial recovery, as impaired domains receive greater attention. In combination, contributions (1) and (2) may lead to the development of an intervention which could be conducted in parallel or in lieu of other treatments for depression. (3) The current study will also improve our understanding of the genomic, neurological and biological correlates of psychosocial and cognitive dysfunction in depression. Taken together, these findings will advance the field of personalized psychiatry by evaluating the relative efficacy of a standard and personalized treatment approach, in addition to testing the overall value of targeting psychosocial deficits in MDD.

ETHICS STATEMENT

This study will be carried out in accordance with the recommendations of the NHMRC national statement on ethical conduct in human research, Royal Adelaide Hospital HREC with written informed consent from all subjects. All subjects will give written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Royal Adelaide Hospital HREC and the University of Adelaide HREC.

AUTHOR CONTRIBUTIONS

BB: primary investigator. BB is involved in study design, recruitment, supervision, and in his capacity as study Doctor. MK: research officer. MK is involved in study design, recruitment, and administering the CERT-D intervention and assessments.

FUNDING

The study is generously supported by the James and Diana Ramsay Foundation, South Australia. The Foundation has had no influence on the topic of the research, the design, the outcomes, analyses, or any other parts of the study. Infrastructure is provided by the University of Adelaide.

REFERENCES

1. World Health Organisation. *Depression and Other Common Mental Disorders*. (2017). Available from: http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2-eng.pdf
2. Baune BT, Renger L. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression – a systematic review. *Psychiatry Res* (2014) 219(1):25–50. doi:10.1016/j.psychres.2014.05.013
3. Godard J, Baruch P, Grondin S, Lafleur MF. Psychosocial and neurocognitive functioning in unipolar and bipolar depression: a 12-month prospective study. *Psychiatry Res* (2012) 196(1):145–53. doi:10.1016/j.psychres.2011.09.013
4. Beblo T, Kater L, Baetge S, Driessen M, Piefke M. Memory performance of patients with major depression in an everyday life situation. *Psychiatry Res* (2017) 248:28–34. doi:10.1016/j.psychres.2016.12.013
5. Elgamal S, McKINNON MC, Ramakrishnan K, Joffe RT, MacQUEEN G. Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study. *Psychol Med* (2007) 37(09):1229–38. doi:10.1017/S0033291707001110
6. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA* (2003) 100(24):14293–6. doi:10.1073/pnas.2336126100
7. Ro E, Clark LA. Psychosocial functioning in the context of diagnosis: assessment and theoretical issues. *Psychol Assess* (2009) 21(3):313. doi:10.1037/a0016611
8. Cacilhas AA, da Silva Magalhães PV, Ceresér KM, Walz JC, Weyne F, Rosa AR, et al. Validity of a short functioning test (FAST) in Brazilian outpatients with bipolar disorder. *Value Health* (2009) 12(4):624–7. doi:10.1111/j.1524-4733.2008.00481.x
9. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clin Pract Epidemiol Mental Health* (2007) 3(1):5. doi:10.1186/1745-0179-3-5
10. Goštautas A, Pranckevičienė A, Matonienė V. Changes in depression and quality of life during inpatient treatment of depression. *Medicina (Kaunas)* (2006) 42(6):472–7.
11. Papakostas GI, Petersen T, Mahal Y, Mischoulon D, Nierenberg AA, Fava M. Quality of life assessments in major depressive disorder: a review of the literature. *Gen Hosp Psychiatry* (2004) 26(1):13–7. doi:10.1016/j.genhosppsych.2003.07.004
12. Baune BT, Air T. Clinical, functional, and biological correlates of cognitive dimensions in major depressive disorder – rationale, design, and characteristics of the cognitive function and Mood Study (CoFaM-Study). *Front Psychiatry* (2016) 7. doi:10.3389/fpsyt.2016.00150
13. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res* (2006) 145(1):39–48. doi:10.1016/j.psychres.2005.11.011
14. Raes F, Williams JMG, Hermans D. Reducing cognitive vulnerability to depression: a preliminary investigation of MEmory Specificity Training (MEST) in inpatients with depressive symptomatology. *J Behav Ther Exp Psychiatry* (2009) 40(1):24–38. doi:10.1016/j.jbtep.2008.03.001
15. Baune BT, Miller R, McAfoose J, Johnson M, Quirk F, Mitchell D. The role of cognitive impairment in general functioning in major depression. *Psychiatry Res* (2010) 176(2):183–9. doi:10.1016/j.psychres.2008.12.001
16. Weightman MJ, Air TM, Baune BT. A review of the role of social cognition in major depressive disorder. *Front Psychiatry* (2014) 5:179. doi:10.3389/fpsyt.2014.00179
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington: American Psychological Association (2013).
18. Garcia-Toro M, Talavera JA, Gonzalez E, Tejada P, Blanco C, Gonzalez A, et al. Audioverbal cognitive dysfunction in depression. Factors involved. *Prog Neuropsychopharmacol Biol Psychiatry* (2003) 27(1):37–42. doi:10.1016/S0278-5846(02)00312-3
19. Mondal S, Sharma VK, Das S, Goswami U, Gandhi A. Neuro-cognitive functions in patients of major depression. *Indian J Physiol Pharmacol* (2007) 51(1):69.
20. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* (2011) 36(12):2452. doi:10.1038/npp.2011.132
21. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev* (2009) 33(3):355–66. doi:10.1016/j.neubiorev.2008.10.005
22. Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M, et al. Association between IL-8 cytokine and cognitive performance in an elderly general population—the MEMO-Study. *Neurobiol Aging* (2008) 29(6):937–44. doi:10.1016/j.neurobiolaging.2006.12.003
23. Baune BT, Ponath G, Rothermundt M, Riess O, Funke H, Berger K. Association between genetic variants of IL-1β, IL-6 and TNF-α cytokines and cognitive performance in the elderly general population of the MEMO-study. *Psychoneuroendocrinology* (2008) 33(1):68–76. doi:10.1016/j.psyneuen.2007.10.002

24. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* (2009) 71(2):171–86. doi:10.1097/PSY.0b013e3181907c1b
25. Wilson CB, Ebenezer PJ, McLaughlin LD, Francis J. Predator exposure/psychosocial stress animal model of post-traumatic stress disorder modulates neurotransmitters in the rat hippocampus and prefrontal cortex. *PLoS One* (2014) 9(2):e89104. doi:10.1371/journal.pone.0089104
26. Lee RS, Hermens DF, Porter MA, Redoblado-Hodge MA. A meta-analysis of cognitive deficits in first-episode major depressive disorder. *J Affect Disord* (2012) 140(2):113–24. doi:10.1016/j.jad.2011.10.023
27. Maples NJ, Velligan DI. Cognitive adaptation training: establishing environmental supports to bypass cognitive deficits and improve functional outcomes. *Am J Psychiatr Rehabil* (2008) 11(2):164–80. doi:10.1080/15487760801963686
28. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* (2011) 12(3):154–67. doi:10.1038/nrn2994
29. Raz G, Winetraub Y, Jacob Y, Kinreich S, Maron-Katz A, Shaham G, et al. Portraying emotions at their unfolding: a multilayered approach for probing dynamics of neural networks. *Neuroimage* (2012) 60(2):1448–61. doi:10.1016/j.neuroimage.2011.12.084
30. Raz G, Jacob Y, Gonen T, Winetraub Y, Flash T, Soreq E, et al. Cry for her or cry with her: context-dependent dissociation of two modes of cinematic empathy reflected in network cohesion dynamics. *Soc Cogn Affect Neurosci* (2014) 9(1):30–8. doi:10.1093/scan/nst052
31. Beck AT. The evolution of the cognitive model of depression and its neurobiological correlates. *Am J Psychiatry* (2008) 165(8):969–77. doi:10.1176/appi.ajp.2008.08050721
32. Joormann J, Vanderlind WM. Emotion regulation in depression the role of biased cognition and reduced cognitive control. *Clin Psychol Sci* (2014) 2(4):402–21. doi:10.1177/2167702614536163
33. Young KD, Erickson K, Nugent AC, Fromm SJ, Mallinger AG, Furey ML, et al. Functional anatomy of autobiographical memory recall deficits in depression. *Psychol Med* (2012) 42(02):345–57. doi:10.1017/S0033291711001371
34. Iacoviello BM, Charney DS. Developing cognitive-emotional training exercises as interventions for mood and anxiety disorders. *Eur Psychiatry* (2015) 30(1):75–81. doi:10.1016/j.eurpsy.2014.09.415
35. Iacoviello BM, Wu G, Alvarez E, Huryk K, Collins KA, Murrough JW, et al. Cognitive-emotional training as an intervention for major depressive disorder. *Depress Anxiety* (2014) 31(8):699–706. doi:10.1002/da.22266
36. Wu D, Chen T, Yang H, Gong Q, Hu X. Verbal responses, depressive symptoms, reminiscence functions and cognitive emotion regulation in older women receiving individual reminiscence therapy. *J Clin Nurs* (Forthcoming 2017). doi:10.1111/jocn.14156
37. Kandalaft MR, Didehbani N, Cullum CM, Krawczyk DC, Allen TT, Tamminga CA, et al. The Wechsler ACS social perception subtest: a preliminary comparison with other measures of social cognition. *J Psychoeduc Assess* (2012) 30(5):455–65. doi:10.1177/0734282912436411
38. Holdnack J, Goldstein G, Drozdick L. Social perception and WAIS-IV performance in adolescents and adults diagnosed with Asperger's syndrome and autism. *Assessment* (2011) 18(2):192–200. doi:10.1177/1073191110394771
39. Szanto K, Dombrovski AY, Sahakian BJ, Mulsant BH, Houck PR, Reynolds CF, et al. Social emotion recognition, social functioning, and attempted suicide in late-life depression. *Am J Geriatr Psychiatry* (2012) 20(3):257–65. doi:10.1097/JGP.0b013e31820eea0c
40. Donges US, Kersting A, Dannlowski U, Lalee-Mentzel J, Arolt V, Suslow T. Reduced awareness of others' emotions in unipolar depressed patients. *J Nerv Ment Dis* (2005) 193(5):331–7. doi:10.1097/01.nmd.0000161683.02482.19
41. Lee L, Harkness KL, Sabbagh MA, Jacobson JA. Mental state decoding abilities in clinical depression. *J Affect Disord* (2005) 86(2):247–58. doi:10.1016/j.jad.2005.02.007
42. Demenescu LR, Kortekaas R, den Boer JA, Aleman A. Impaired attribution of emotion to facial expressions in anxiety and major depression. *PLoS One* (2010) 5(12):e15058. doi:10.1371/journal.pone.0015058
43. Bourke C, Douglas K, Porter R. Processing of facial emotion expression in major depression: a review. *Aust N Z J Psychiatry* (2010) 44(8):681–96. doi:10.3109/00048674.2010.496359
44. Brewer N, Young RL, Barnett E. Measuring theory of mind in adults with autism spectrum disorder. *J Autism Dev Disord* (2017) 47(7):1927–41. doi:10.1007/s10803-017-3080-x
45. Dziobek I, Fleck S, Kalbe E, Rogers K, Hassenstab J, Brand M, et al. Introducing MASC: a movie for the assessment of social cognition. *J Autism Dev Disord* (2006) 36(5):623–36. doi:10.1007/s10803-006-0107-0
46. Baune BT, Fuhr M, Air T, Hering C. Neuropsychological functioning in adolescents and young adults with major depressive disorder – a review. *Psychiatry Res* (2014) 218(3):261–71. doi:10.1016/j.psychres.2014.04.052
47. Motter JN, Pimontel MA, Rindskopf D, Devanand DP, Doraiswamy PM, Sneed JR. Computerized cognitive training and functional recovery in major depressive disorder: a meta-analysis. *J Affect Disord* (2016) 189:184–91. doi:10.1016/j.jad.2015.09.022
48. Vieta E, Torrent C. Functional remediation: the pathway from remission to recovery in bipolar disorder. *World Psychiatry* (2016) 15(3):288–9. doi:10.1002/wps.20351
49. Combs DR, Adams SD, Penn DL, Roberts D, Tiegreen J, Stem P. Social Cognition and Interaction Training (SCIT) for inpatients with schizophrenia spectrum disorders: preliminary findings. *Schizophr Res* (2007) 91(1):112–6. doi:10.1016/j.schres.2006.12.010
50. Amare AT, Schubert KO, Baune BT. Pharmacogenomics in the treatment of mood disorders: strategies and opportunities for personalized psychiatry. *EPMA J* (2017) 8(3):211–27. doi:10.1007/s13167-017-0112-8
51. Morimoto SS, Wexler BE, Alexopoulos GS. Neuroplasticity-based computerized cognitive remediation for geriatric depression. *Int J Geriatr Psychiatry* (2012) 27(12):1239–47. doi:10.1002/gps.3776
52. Morimoto SS, Wexler BE, Liu J, Hu W, Seirup J, Alexopoulos GS. Neuroplasticity-based computerized cognitive remediation for treatment-resistant geriatric depression. *Nat Commun* (2014) 5:4579. doi:10.1038/ncomms5579
53. Sheehan D, Lecrubier Y, Sheehan KH, Sheehan K, Amorim P, Janavs J, et al. Diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* (1998) 59:22–33.
54. Sheehan DV, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, et al. Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). *J Clin Psychiatry* (2010) 71(3):313–26. doi:10.4088/JCP.09m05305whi
55. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* (1979) 134(4):382–9. doi:10.1192/bjp.134.4.382
56. Kinsinger SW, Lattie E, Mohr DC. Relationship between depression, fatigue, subjective cognitive impairment, and objective neuropsychological functioning in patients with multiple sclerosis. *Neuropsychology* (2010) 24(5):573. doi:10.1037/a0019222
57. Crawford JR, Henry JD. The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. *Br J Clin Psychol* (2004) 43(3):245–65. doi:10.1348/0144665031752934
58. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* (1988) 54(6):1063. doi:10.1037/0022-3514.54.6.1063
59. Williams JBW. *Structured Interview Guide for the Hamilton Depression and Anxiety Scales (SIGH-AD)*. New York: New York State Psychiatric Institute (1988).
60. Prasad M, Wahlqvist P, Shikiar R, Shih YCT. A review of self-report instruments measuring health-related work productivity. *Pharmacoeconomics* (2004) 22(4):225–44. doi:10.2165/00019053-200422040-00002
61. Reilly MC, Bracco A, Ricci JF, Santoro J, Stevens T. The validity and accuracy of the work productivity and activity impairment questionnaire–irritable bowel syndrome version (WPAI: IBS). *Aliment Pharmacol Ther* (2004) 20(4):459–67. doi:10.1111/j.1365-2036.2004.02091.x
62. Wagnild G. A review of the Resilience Scale. *J Nurs Meas* (2009) 17(2):105–13. doi:10.1891/1061-3749.17.2.105
63. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas* (1993) 1:165–78.
64. Ahern NR, Kiel EM, Lou Sole M, Byers J. A review of instruments measuring resilience. *Issues Compr Pediatr Nurs* (2006) 29(2):103–25. doi:10.1080/01460860600677643
65. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatr Med* (1997) 27(2):93–105. doi:10.2190/T8EM-C8YH-373N-1UWD

66. Leon AC, Shear MK, Portera L, Klerman GL. Assessing impairment in patients with panic disorder: the Sheehan Disability Scale. *Soc Psychiatry Psychiatr Epidemiol* (1992) 27(2):78–82. doi:10.1007/BF00788510
67. Larson GE, Alderton DL, Neideffer M, Underhill E. Further evidence on dimensionality and correlates of the cognitive failures questionnaire. *Br J Psychol* (1997) 88(1):29–38. doi:10.1111/j.2044-8295.1997.tb02618.x
68. Mueller ST, Piper BJ. The psychology experiment building language (PEBL) and PEBL test battery. *J Neurosci Methods* (2014) 222:250–9. doi:10.1016/j.jneumeth.2013.10.024
69. Baddeley AD. Working memory. *Philos Trans R Soc Lond B Biol Sci* (1983) 302:311–24. doi:10.1098/rstb.1983.0057
70. Artiges E, Salamé P, Recasens C, Poline JB, Attar-Levy D, De la Raillère A, et al. Working memory control in patients with schizophrenia: a PET study during a random number generation task. *Am J Psychiatry* (2000) 157(9):1517–9. doi:10.1176/appi.ajp.157.9.1517
71. Knight MJ, Tlauka M. Interactivity in map learning: the effect of cognitive load. *Spat Cogn Comput* (2017) 17(3):185–98. doi:10.1080/13875868.2016.1211661
72. Knight MJ, Tlauka M. Map learning and working memory: multimodal learning strategies. *Q J Exp Psychol* (2017):1–45. doi:10.1080/17470218.2017.1326954
73. Vandierendonck A, Kemps E, Fastame MC, Szmalec A. Working memory components of the Corsi blocks task. *Br J Psychol* (2004) 95(1):57–79. doi:10.1348/000712604322779460
74. Yang TX, Allen RJ, Gathercole SE. Examining the role of working memory resources in following spoken instructions. *J Cogn Psychol* (2016) 28(2):186–98. doi:10.1080/20445911.2015.1101118
75. Guilera G, Pino O, Gómez-Benito J, Rojo JE, Vieta E, Tabarés-Seisdedos R, et al. Clinical usefulness of the screen for cognitive impairment in psychiatry (SCIP-S) scale in patients with type I bipolar disorder. *Health Qual Life Outcomes* (2009) 7(1):28. doi:10.1186/1477-7525-7-28
76. Murray LA, Whitehouse WG, Alloy LB. Mood congruence and depressive deficits in memory: a forced-recall analysis. *Memory* (1999) 7(2):175–96. doi:10.1080/741944068
77. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry* (2001) 42(2):241–51. doi:10.1111/1469-7610.00715
78. Tchanturia K, Doris E, Fleming C. Effectiveness of cognitive remediation and emotion skills training (CREST) for anorexia nervosa in group format: A naturalistic pilot study. *Eur Eat Disord Rev* (2014) 22(3):200–5. doi:10.1002/erv.2287
79. Lahera G, Benito A, Montes JM, Fernandez-Liria A, Olbert CM, Penn DL. Social cognition and interaction training (SCIT) for outpatients with bipolar disorder. *J Affect Disord* (2013) 146(1):132–6. doi:10.1016/j.jad.2012.06.032
80. Roberts DL, Combs DR, Willoughby M, Mintz J, Gibson C, Rupp B, et al. A randomized, controlled trial of Social Cognition and Interaction Training (SCIT) for outpatients with schizophrenia spectrum disorders. *Br J Clin Psychol* (2014) 53(3):281–98. doi:10.1111/bjc.12044

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer MJ and handling editor declared their shared affiliation.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 06 April 2018
doi: 10.3389/fpsyt.2018.00120

Impaired Cognitive Control of Emotional Conflict in Trait Anxiety: A Preliminary Study Based on Clinical and Non-Clinical Individuals

*Yongju Yu[1], Chenggang Jiang[2], Haiyan Xu[1], Qian Yang[1], Jiawen Li[1], Yuanyuan Xu[1], Wenjun Xiang[3], Li Peng[1], Botao Liu[1], Fang Lv[3] and Min Li[1]**

[1] Department of Military Psychology, School of Psychology, Third Military Medical University, Chongqing, China, [2] Daping Hospital, Third Military Medical University, Chongqing, China, [3] School of Nursing, Third Military Medical University, Chongqing, China

Background: It has been observed that trait anxiety easily leads to conflict maladaptation under conflict circumstances. However, it remains unclear whether the precise neural mechanisms underlying the effects of high trait anxiety (HTA) on cognitive control are consistent in high trait anxious individuals, with and without anxiety disorders.

Methods: The present study recruited 29 healthy volunteers with low trait anxiety (LTA), 37 healthy volunteers with HTA, and 23 patients with generalized anxiety disorder (GAD). All participants completed demographic information and self-report measures of trait anxiety and depression. Then, they performed the emotional flanker task with event-related potentials (ERPs) recorded.

Results: Behavioral data manifested that, relative to LTA individuals, GAD patients displayed prolonged response times and increased error rates, while HTA individuals showed intact response times and accuracies. Event-related potential (ERP) data revealed that HTA individuals exhibited a trend toward more negative N2 amplitudes for conflict detection. By contrast, both HTA and GAD individuals displayed decreased P3 amplitudes for conflict resolution. ERP results indicated that both HTA and GAD individuals exhibited conflict maladaptation on the N2 amplitude. Correlation analyses also showed that the increased anxiety symptoms were associated with longer reaction times, more error rates, lower P3 amplitudes, and more perturbations in conflict adaptation on reaction times and N2 amplitudes.

Conclusion: Our results demonstrated a severely impaired cognitive control in GAD patients while a moderately impaired cognitive control in HTA individuals. Trait anxiety can indeed serve as a predominant factor at the onset and in the maintenance of GAD. Therefore, the trait anxiety reducing strategies may provide significant therapeutic gains.

Keywords: trait anxiety, conflict detection, conflict resolution, conflict adaptation effect, generalized anxiety disorder

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Rebecca Strawbridge,
King's College London,
United Kingdom
Michele Fornaro,
Columbia University, United States

****Correspondence:***
Min Li
limin52267@tmmu.edu.cn

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *22 January 2018*
Accepted: *22 March 2018*
Published: *06 April 2018*

Citation:
Yu Y, Jiang C, Xu H, Yang Q, Li J, Xu Y, Xiang W, Peng L, Liu B, Lv F and Li M (2018) Impaired Cognitive Control of Emotional Conflict in Trait Anxiety: A Preliminary Study Based on Clinical and Non-Clinical Individuals. Front. Psychiatry 9:120. doi: 10.3389/fpsyt.2018.00120

INTRODUCTION

Increasing evidence has demonstrated that trait anxiety is related to impaired executive control of attention (1). The attentional control theory (ACT) proposed that anxiety is closely related to cognitive deficits (2), which makes it difficult for anxious individuals to efficiently inhibit distraction information. Therefore, anxiety has been considered to be able to inhibit attention,

and it may be harder for trait anxious individuals to suppress threat-related irrelevant stimuli (2, 3). These deficits primarily affect processing efficiency, without adverse effects on performance effectiveness (1). Thus, in some cases participants with high anxiety show no greater evidence of disrupted attentional control behaviorally, but need to use more cognitive resources to perform at a level-standard relative to persons with low anxiety. These viewpoints, however, have not been systematically tested.

The face flanker paradigm allows for the efficient investigation of trait anxious individuals' patterns of cognitive control, thereby illuminating how attention allocation is impacted by interactions between the target and distractor (4, 5). Reaction time interference by emotionally incongruent stimuli was observed in almost every individual (6, 7). That is, participants exhibit faster response speed when the distractor expressions are identical with the target expression. A large number of studies also showed that the emotional conflict generated by the previous incongruent trial can activate a regulatory mechanism which helps individuals to improve emotional conflict regulation on the current incongruent trial (8–10). Therefore, task performance was optimized. Likewise, performance on postcongruent congruent trials is often superior to that on postincongruent congruent trials. This across-trial effect has been termed as "emotional conflict adaptation" (11).

Event-related potential (ERP) studies have found that, in the conflict control processing, N2 and P3 components are associated with conflict detection and conflict resolution, respectively (12, 13). The conflict N2 component is a negative deflection peaking at about 200–300 ms after stimulus onset. It is derived from the anterior cingulate cortex and serves as an indicator of response conflict (10). It has been demonstrated that the N2 component on incompatible trials is larger than that on compatible trials (14, 15). When participants are attending more to flanker information than target information, a larger N2 amplitude will be elicited (16, 17). Empirical research found that, compared to healthy individuals, patients with generalized anxiety disorder (GAD) showed decreased N2 amplitudes for conflict adaptation in non-emotional flanker task that may be influenced by compensatory activity (18).

The P3 component is a positive-going ERP that peaks approximately 300–500 ms after stimulus presentation which serves as a marker of the active suppression of a motor response (i.e., conflict resolution) (19, 20). Most studies assume the flanker P3 to be functionally similar to the P3a (21, 22), reflecting activation in prefrontal brain (23). Research suggested that the P3 component elicited by stimulus conflict is larger for incongruent trials than that for congruent ones (13, 24) and proposed that the larger P3 amplitude elicited by incongruent trials is related to a more careful assessment of the stimulus to determine the correct response. According to previous studies, the P3 is reduced in clinical groups such as those with schizophrenia and ADHD (25, 26). Longer P3 latency elicited by incongruent trials implies the increased stimulus evaluation or categorization time (13, 27). These behavioral and neural markers of conflict control can capture subtle differences in cognitive processing and serve as ideal indicators for identifying cognitive deficits in trait anxiety.

Although dysfunctional forms of cognitive processing in trait anxiety have been well evidenced, more extensive studies are necessary, because findings related to emotional regulation mainly restricted to persons diagnosed with GAD. Recent research in non-clinical anxiety revealed that there are different components of anxiety-related cognitive control, which have different clinical implications (29). However, so far, few studies have directly examined the mechanisms responsible for the effect of trait anxiety on cognitive control based on clinical and non-clinical individuals simultaneously. Therefore, in this study, healthy individuals with low levels of trait anxiety [low trait anxiety (LTA)], healthy individuals with high levels of trait anxiety (HTA), and trait anxious patients with a diagnosis of GAD were recruited and emotional flanker task was adopted to examine two issues (1): how trait anxiety affects processing efficiency and performance effectiveness for HTA and GAD individuals separately? (2) Whether trait anxiety inevitably elicits conflict maladaptation. Based on empirical and theoretical evidence, we hypothesize that: (1) relative to LTA individuals, HTA ones should display at a level-standard performance effectiveness at the expense of processing efficiency, while GAD patients have shortfalls in both performance effectiveness and processing efficiency (2). For both HTA and GAD individuals, trait anxiety will impair conflict detection and conflict resolution, thereby leading to conflict maladaptation.

MATERIALS AND METHODS

Participants

This study was approved by the ethics committee of Third Military Medical University of China. The total sample was consisted of three subgroups: LTA, HTA, and GAD. All of them provided written consent after a detailed explanation of the study aims and procedures. Participants received 50 RMB for their time.

Initially, through announcements (intranet, Internet, and local poster), 1,539 healthy persons aged from 16 to 45 were recruited to take part in a mass screening by assessing their levels of trait anxiety (30, 31). Subsequently, persons in the lower 27% of the trait anxiety distribution [State-Trait Anxiety Inventory (STAI_T) $\leq$ 33] were assigned to the LTA group, and the ones in the higher 27% of the trait anxiety distribution (STAI_T $\geq$ 40) were assigned to the HTA group.

Individuals who were willing to take part in the following experiments were asked to complete the Center for Epidemiologic Studies Depression Scale (CES-D) (32), fill basic personal information, and report the past history of disease. The inclusion criteria in the present study for the normal participants were as follows: (1) no less than 9 years of education; (2) normal or corrected-to-normal vision; (3) provided informed consent to take part in the present research; (4) no evidence of substance abuse or dependence in the past 3 months; and (5) no mental and cognitive disorders or brain injury.

High trait anxious patients diagnosed with GAD were recruited from the outpatient clinic of Xinqiao Hospital and Daping Hospital of Chongqing, China. Prior to participation, they were diagnosed

by two licensed clinical psychologists. Diagnoses were confirmed using the Chinese Version of Mini-International Neuropsychiatric Inventory (33, 34). Then, they completed measures of trait anxiety, depression, and detailed information regarding the inclusion criteria. The inclusion criteria for the GAD participants were as follows: (1) aged between 16 and 45 years; (2) no less than 9 years of education; (3) normal or corrected-to-normal vision; (4) with heightened level of trait anxiety (STAI_T $\geq$ 40); (5) no evidence of substance abuse or dependence in the past 3 months; (6) no history of schizophrenia, bipolar disorder, organic mental disorder or brain injury; and (7) no treatment of electric shock, repetitive transcranial magnetic stimulation, deep brain electrical stimulation, or other electromagnetic techniques in the past 6 months. Study enrollment included 29 LTA individuals, 37 HTA individuals, and 23 patients with GAD.

Materials and Tasks

Self-Report Measures

The trait subscale of Spielberger's STAI_T (30) was used to measure the level of trait anxiety. This subscale consists of 20 items that can indicate individuals' tendency to perceive stressful situations as dangerous or threatening. Answers were given on a 4-point Likert scale. This measure has adequate psychometric properties. Internal consistency was Cronbach's alpha = 0.950 for STAI_T in the current study. The CES-D (32) was adopted to measure the level of depression. The CES-D is a self-report scale specifically designed for epidemiological studies to assess the presence of clinical and non-clinical symptoms of depression in the general population. The CESD consists of 20 items with adequate psychometric properties (35). Internal consistency for the sample was Cronbach's alpha = 0.953 for CES-D in this study.

Apparatus and Stimuli

All stimuli were presented on a 17-inch Lenovo CRT monitor with a resolution of 1,024 × 768 pixels. E-Prime 2.0 Software Package was used to run the emotional flanker task. Participants were seated about 70 cm from the computer screen and performed emotional flanker task.

Emotional Flanker Task

Photos of 24 different people (12 female, 12 male) showing happy or angry emotional expressions (the ratio was 1:1) were chosen from the standardized native Chinese Affective Picture System (CAPS) (36). On each trial, the target face (2.05° × 2.37°) was surrounded by two flanker faces that owned either congruent or incongruent emotion with the target on right and left sides. Target and flankers always appeared at the same positions on the black background. Participants were instructed to respond to the emotion of the central face by pressing "f" button for happy faces and "j" for angry ones while ignoring the flanker faces. Participants were encouraged to respond to the stimuli as quickly and accurately as possible. There was one practice block and four experimental blocks. The task consisted of 25 practice trials and 196 experimental trials. Four photos used in the practice block did not disappear in the following experimental blocks. Each trial began with a fixation cross displayed on the center of the screen for 500 ms. The fixation cross was then replaced by a target face with two flankers located at the left and right of each target. Stimuli were presented in a pseudorandom order and remained on the screen until the participant responded. A varying interstimulus interval was set between 800 and 1,500 ms. There was a break between each block. Completion of the experiment required about 15 min. The schematic experimental procedure of the emotional flanker task is illustrated in **Figure 1**.

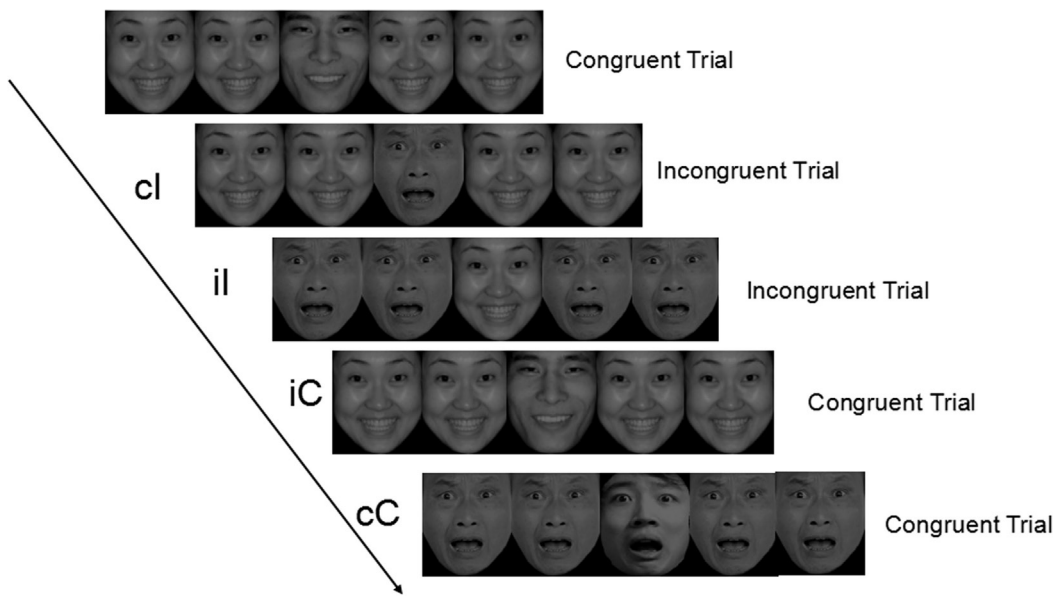

FIGURE 1 | Graphical representation of trials and experimental conditions. cC, congruent trials preceded by congruent trials; cI, incongruent trials preceded by congruent trials; iI, incongruent trials preceded by incongruent trials; iC, congruent trials preceded by incongruent trials.

The flanker task comprised four types of experimental conditions according to the match between the current and the previous trial: congruent—Congruent (cC), congruent—Incongruent (cI), incongruent—Incongruent (iI), and incongruent—Congruent (iC). According to Nieuwenhuis et al. (37), index of conflict adaptation effect (CAE) on RT (CAE_{RT}) can be computed as follows: $CAE_{RT} = (RT_{cI} - RT_{cC}) - (RT_{iI} - RT_{iC})$. Formulas used to calculate CAEs on error rates, N2 and P3 components are similar to the aforementioned one.

ERP Recording and Analysis

The experiment was conducted in a dimly lit and electrically shielded room. Each participant was asked to sit still and minimize blinks and movements during electroencephalography (EEG) recording. A high-density EEG recording was acquired with a QuickAmp amplifier using 64 Ag/AgCl electrodes. All electrodes were referenced on line to the Cz position with a ground electrode on AFz. Horizontal and vertical electrooculogram signals were recorded with four bipolar electrodes placed on the outer canthus of each eye as well as above and below the right eye. The EEG activity was amplified using 0.01–100 Hz band-passed filters and sampled at 1,000 Hz. Impedance was kept below 5 kΩ for all electrodes.

MATLAB 2013b (MathWorks, USA) and the EEGLAB13.4.4b toolbox (38) were used to conduct offline EEG analyses. For offline analysis, the EEG data were filtered using a bandpass between 0.5 and 30 Hz and re-referenced to the average of the two mastoids. Then, the data were segmented into epochs ranging from 200 ms prestimulus to 700 ms post-stimulus. Baseline correction was performed using the prestimulus interval. Epochs were rejected if the voltage deviated more than 5 SD values of the probability distribution. Finally, the runica function of EEGLAB was used to perform independent components (ICs). ICs identified as muscle activity, eye movements, eye blinks, or other types of noise were removed from the EEG signal.

The mean amplitudes were calculated from latency windows of ±10 ms around the maximum peaks latencies identified from the mean global field power (28) that were obtained including all participants and all conditions for each type of stimulus. Two late ERP components were used to test predictions from the conflict monitoring model: the frontal N2 and the central P3. The N2 component was measured as the most negative local amplitude between 200 and 300 ms post-stimulus on the average of five fronto-central electrodes (Fz, FCz, FC1, FC2, and Cz). The P3 component was measured as the most positive local amplitude between 300 and 500 ms post-stimulus on the average of five centro-parietal electrodes (Cz, CPz, CP1, CP2, and Pz).

Data Analysis

Outliers were removed in keeping with recommendations from Ratcliff (39). Participants with mean accuracy less than 75% were excluded from analysis, which resulted in the exclusion of one participant from the LTA group, two participants from the HTA group, and two participants from the GAD group. Trials that involved incorrect responses and RTs exceeding 3 SD from mean RTs (1.63%) were eliminated from the data. Besides that, 6 participants were excluded due to their EEG data loss resulting from machine fault, and 7 participants were excluded because of too few effective ERP epochs (no less than 20 each condition). Finally, there are 84 valid participants for the behavioral data and 66 valid participants for the ERP data.

IBM SPSS software V18 (IBM Corp., Armonk, NY, USA) was used for further statistical analyses. Controlling for three socio-demographic variables (age, gender, and educational level), a series of 3 (group: LTA, HTA, and GAD) × 2 (trial type: congruent and incongruent) repeated measures analysis of variance (ANOVA) were conducted on mean RTs and error rates as well as on the latencies and amplitudes of N2 and P3 components in order to assess the main effects and interactions. The indexes of CAE on behavior and ERP data were calculated separately according to the calculation formula of CAE. Subsequently, one-way ANOVA was carried out to examine the study group difference. According to the Greenhouse–Geisser method, the degrees of freedom for all repeated measures ANOVAs were corrected. The correlations between trait anxiety and RTs, error rates, and ERP data were also examined.

Using Lilliefors significance correction, Kolmogorov–Smirnov statistic analysis verified that behavioral results and ERP data approximated normal distribution (for complete sample or each group separately, $Ps = 0.239–0.101 > 0.05$). For all analyses in this study, the significance level was set at $P < 0.05$. Results are presented as mean ± *SD*.

RESULTS

Demographics and Self-Report Data

Table 1 shows participant characteristics. The LTA, HTA, and GAD groups did not significantly differ in gender, age or education

TABLE 1 | Demographic and questionnaire data for participants (mean ± *SD*).

		Low trait anxiety (29)	High trait anxiety (36)	Generalized anxiety disorder (21)	*P*
Education	Less than high school	0	1 (2.9%)	3 (14.3%)	0.100
	Completed high school	25 (89.3%)	24 (68.6%)	7 (33.3%)	
	Junior college or Bachelor's degree	3 (10.7%)	6 (17.1%)	10 (47.6%)	
	Graduate	0	4 (11.4%)	1 (4.8%)	
% Female		21.43	19.44	42.86	0.189
Age		23.85 ± 4.10	24.11 ± 6.16	27.19 ± 7.11	0.161
STAI-T		28.32 ± 3.43	46.49 ± 5.11	57.86 ± 8.31	<0.001
CES-D		1.25 ± 1.71	13.51 ± 9.92	31.14 ± 13.67	<0.001

which indicated that these groups well matched with respect to demographic variables. As expected, there were significant group differences in trait anxiety and depression (*Ps* < 0.001). Specifically, participants with GAD had significantly higher levels of STAI-T and CES-D compared to those of LTA and HTA groups (*Ps* < 0.001), while participants in the HTA group had significantly greater STAI-T and CES-D scores than those of the LTA group ($P < 0.001$).

Behavioral Results

Descriptives of mean RTs and error rates in each condition in the emotional flanker task are presented in **Table 2**. Controlling for three sociodemographic variables, a two-way repeated measures ANOVA on mean RTs was conducted with group as the between-subjects variable and trial type as the within-subjects variable. Neither the interaction of group and trial type [$F(2,81) = 0.251$, $P = 0.779$, $\eta_P^2 = 0.006$], nor the main effect of trial type [$F(1,81) = 0.467$, $P = 0.496$, $\eta_P^2 = 0.006$] reached statistical significance. Nevertheless, a significant main effect of group was found [$F(2,81) = 51.299$, $P < 0.001$, $\eta_P^2 = 0.568$]. *Post hoc* comparisons between groups showed that RTs of the GAD group (928.84 ± 140.86) were significantly longer than those of the LTA (630.31 ± 82.83, $P < 0.001$) and HTA groups (655.06 ± 93.18, $P < 0.001$). No significant difference was found between the LTA and HTA groups ($P = 0.380$).

Similar results were obtained by a two-way repeated measures ANOVA on error rates. Both the interaction of group and trial type [$F(2,81) = 1.594$, $P = 0.210$, $\eta_P^2 = 0.039$] and the main effect of trial type [$F(1,81) = 0.366$, $P = 0.547$, $\eta_P^2 = 0.005$] far from significance. However, the main effect of group was found to be significant [$F(2,81) = 3.904$, $P = 0.024$, $\eta_P^2 = 0.091$]. *Post hoc* multiple comparisons showed that error rates for the GAD group (2.51 ± 1.95) were significantly larger than those for the LTA (1.38 ± 1.68, $P = 0.023$) and HTA groups (1.37 ± 1.85, $P = 0.009$), and no significant difference was observed between the LTA and HTA groups ($P = 0.795$).

Also, the indexes of CAE on RTs and error rates were calculated. After controlling for three sociodemographic variables, a one-way ANOVA was performed to check the group difference in CAE. There was no significant difference among these three groups in CAE of RTs, $F(2,81) = 0.903$, $P = 0.410$. A similar result was observed in CAE of error rates, $F(2,81) = 1.305$, $P = 0.277$.

TABLE 2 | Mean RTs and error rates in emotional Flanker task (mean ± SD).

	LTA	HTA	GAD
Congruent (RT)	637.41 ± 88.88	656.75 ± 92.42	930.40 ± 149.09†‡
Incongruent (RT)	627.92 ± 83.36	653.35 ± 94.82	909.84 ± 150.00†‡
Congruent (error rate)	1.49 ± 1.83	1.31 ± 1.96	2.13 ± 2.04‡
Incongruent (error rate)	1.30 ± 2.04	1.43 ± 2.01	2.88 ± 2.42†‡
cC (RT)	635.56 ± 89.43	659.35 ± 97.20	937.45 ± 150.72†‡
cI (RT)	629.83 ± 86.54	650.85 ± 99.01	926.18 ± 158.99†‡
iC (RT)	639.19 ± 89.89	654.23 ± 91.10	923.76 ± 153.92†‡
iI (RT)	625.89 ± 82.75	656.02 ± 94.96	927.78 ± 135.15†‡
Conflict adaptation effect (CAE) (RT)	7.57 ± 30.30	−10.29 ± 46.17	−15.28 ± 86.76
cC (error rate)	1.04 ± 1.65	1.43 ± 2.46	1.98 ± 2.33
cI (error rate)	1.48 ± 2.83	1.31 ± 1.83	2.68 ± 2.56†‡
iC (error rate)	1.93 ± 2.66	1.19 ± 2.16	2.28 ± 2.79‡
iI (error rate)	1.12 ± 1.84	1.55 ± 2.44	2.90 ± 3.20†‡
CAE (error rate)	1.26 ± 3.60	−0.48 ± 2.67	−0.10 ± 4.91

LTA, low trait anxiety; HTA, high trait anxiety; GAD, generalized anxiety disorder; cC, congruent trials preceded by congruent trials; cI, incongruent trials preceded by congruent trials; iI, incongruent trials preceded by incongruent trials; iC, congruent trials preceded by incongruent trials.

†There was a statistically significant difference between this group and the LTA group (P < 0.05).

‡There was a statistically significant difference between this group and the HTA group (P < 0.05).

Sociodemographic variables were included as covariates for all analyses.

ERP Data

Figure 2 shows stimulus-locked ERPs for compatible and incompatible stimuli from midline electrode sites (FCz, Cz, CPz, and Pz). Peak amplitudes and latencies for N2 and P3 components are listed in **Table 3**.

After controlling for three sociodemographic variables, a two-way repeated measures ANOVA on N2 amplitude showed no significant main effect of group [$F(2,63) = 1.082$, $P = 0.346$, $\eta_P^2 = 0.035$] or trial type [$F(1,63) = 0.254$, $P = 0.616$, $\eta_P^2 = 0.004$]. However, the interaction effect of group and trial type yielded a clear tendency to significance [$F(2,63) = 2.898$, $P = 0.063$, $\eta_P^2 = 0.008$]. After controlling for sociodemographic variables, multiple comparisons showed that HTA individuals had more negative N2 peak amplitudes (−2.58 ± 3.50) relative to GAD patients (−0.29 ± 2.85, $P = 0.039$) for incompatible trials. N2 amplitude of the LTA group (−1.66 ± 3.22) did not differ from those of the HTA and GAD groups ($P = 0.428$, $P = 0.184$, respectively). No group difference was observed for compatible trials on N2 amplitude ($P > 0.05$). For the N2 latency, main effects of group [$F(2,63) = 2.143$, $P = 0.126$, $\eta_P^2 = 0.067$] and trial type [$F(1,63) = 1.392$, $P = 0.243$, $\eta_P^2 = 0.023$], and the interaction effect [$F(2,63) = 2.194$, $P = 0.144$, $\eta_P^2 = 0.035$] were not statistically significant.

Likewise, P3 amplitude and latency were separately subjected to repeated measures ANOVAs. For the P3 amplitude, after controlling for sociodemographic covariates, neither the interaction effect [$F(2,63) = 2.341$, $P = 0.105$, $\eta_P^2 = 0.072$] nor the main effect of trial type [$F(1,63) = 0.001$, $P = 0.972$, $\eta_P^2 = 0.001$] reached significance. However, we found a significant main effect of group [$F(2,63) = 8.268$, $P = 0.001$, $\eta_P^2 = 0.216$] such that the LTA group exhibited more positive P3 amplitudes (9.94 ± 0.60) than the HTA and GAD groups (amplitude = 7.01 ± 0.59, $P = 0.001$; amplitude = 6.52 ± 0.66, $P < 0.001$, respectively). No significant difference was observed between the HTA and GAD groups ($P = 0.553$). For the P3 latency, it was showed that the main effect of group [$F(2,63) = 0.182$, $P = 0.672$, $\eta_P^2 = 0.003$], the main effect of trial type [$F(1,63) = 0.540$, $P = 0.468$, $\eta_P^2 = 0.009$], and the interaction effect [$F(2,63) = 0.348$, $P = 0.708$, $\eta_P^2 = 0.011$] were far from statistical significance.

We also calculated the indexes of CAE on N2 and P3. To check whether the CAE was influenced by trait anxiety, one-way ANOVAs were separately performed for N2 and P3 amplitudes and latencies after controlling for age, gender, and educational level. There was a significant difference in CAE on the N2 amplitude across study groups [$F(2,63) = 4.598$, $P = 0.014$, $\eta_P^2 = 0.133$].

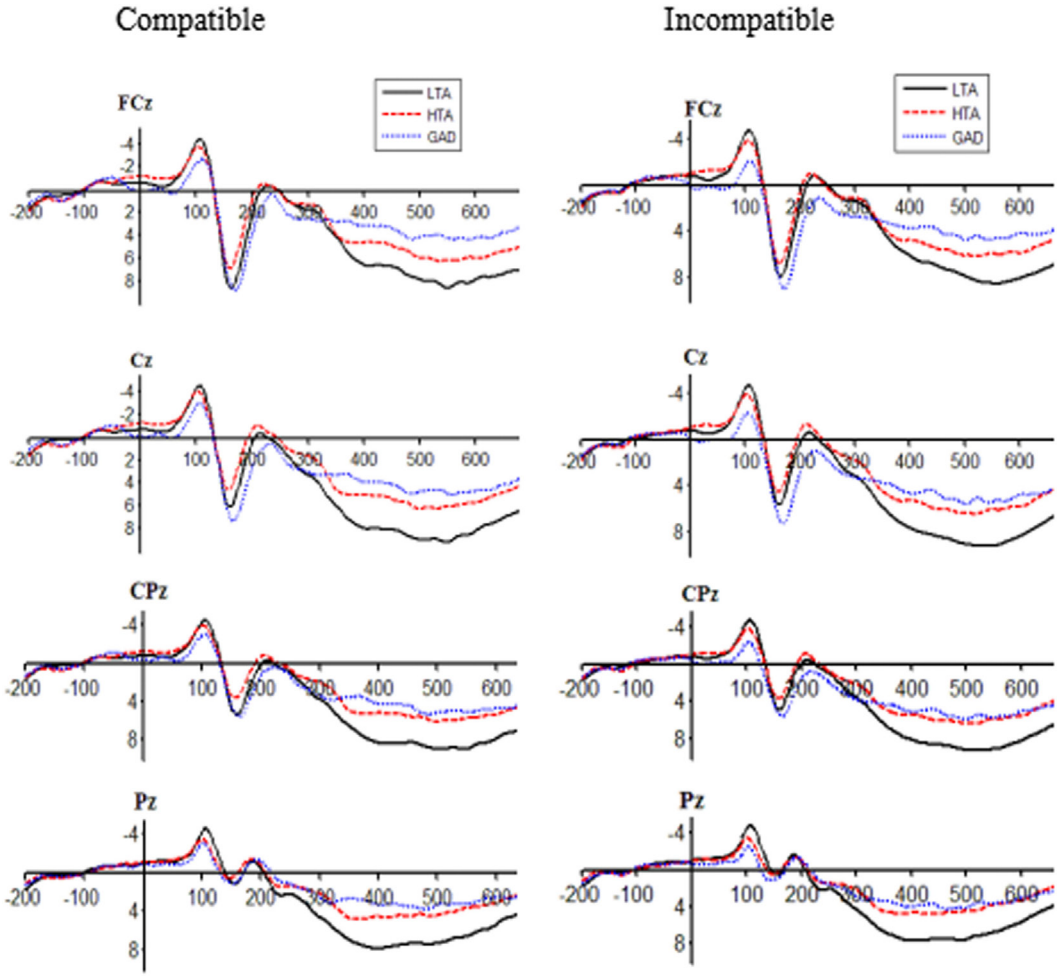

FIGURE 2 | Stimulus-locked event-related potentials for the low trait anxiety (LTA), high trait anxiety (HTA), and generalized anxiety disorder (GAD) groups in compatible and incompatible conditions at FCz, Cz, CPz, and Pz sites.

TABLE 3 | Amplitude (microvolts) and latency (milliseconds) of event-related potential components in emotional Flanker task (mean ± SD).

	LTA (n = 23)	HTA (n = 24)	GAD (n = 19)
Compatible_N2 amplitude	−1.66 ± 3.22	−2.29 ± 3.69	−0.97 ± 2.87
Incompatible_N2 amplitude	−1.78 ± 3.65	−2.58 ± 3.50	−0.29 ± 2.85
Compatible_N2 latency	221.60 ± 20.67	218.87 ± 19.10	226.79 ± 20.88
Incompatible_N2 latency	216.82 ± 19.73	216.11 ± 19.74	229.58 ± 20.42
Compatible_P3 amplitude	10.09 ± 3.54	6.97 ± 2.80	6.31 ± 2.56
Incompatible_P3 amplitude	9.79 ± 3.33	7.05 ± 2.84	6.73 ± 2.34
Compatible_P3 latency	404.53 ± 67.42	423.04 ± 54.59	432.75 ± 50.95
Incompatible_P3 latency	401.75 ± 54.65	420.54 ± 44.62	434.57 ± 48.45

LTA, low trait anxiety; HTA, high trait anxiety; GAD, generalized anxiety disorder.

Post hoc multiple comparisons showed that the LTA group had a larger index of CAE on the N2 amplitude (0.57 ± 2.22) relative to the HTA (−1.34 ± 2.85, $P = 0.012$) and GAD groups (−1.90 ± 2.57, $P = 0.011$). By contrast, indexes of CAE on N2 latency, P3 amplitude, and P3 latency did not vary across study groups ($P = 0.228$, $P = 0.537$, $P = 0.370$, respectively).

Correlation Analyses

To examine the relationship between trait anxiety scores and behavior data, N2 and P3 components across a range of symptom severity, we included all participants in correlation analyses. Scores of trait anxiety were significantly related to RTs, Pearson's $r(84) = 0.602$, $P < 0.001$. A similar result was obtained between scores of trait anxiety and error rates $r(84) = 0.226$, $P = 0.038$. On the other hand, trait anxiety was not related with N2 component [$r(66) = 0.126$, $P = 0.314$ for N2 amplitude; $r(66) = 0.175$, $P = 0.158$ for N2 latency]. HTA is associated with decreased P3 amplitude, $r(66) = -0.465$, $P < 0.001$, but not for trait anxiety and P3 latency, $r(66) = 0.209$, $P = 0.091$.

Associations between trait anxiety scores and the indexes of CAE for behavioral results and ERP data were also assessed by correlation analyses. Higher trait anxiety scores were associated with smaller CAE on RTs, Pearson's $r(84) = -0.219$, $P = 0.046$, but not on error rates, $r(84) = 0.165$, $P = 0.134$. In addition, there was a significant correlation between trait anxiety and CAE on N2 amplitude, $r(66) = -0.356$, $P = 0.003$, indicating decreased

conflict adaptation for individuals with higher trait anxiety. However, no significant correlation was found between trait anxiety and the indexes of CAE on N2 latency, P3 amplitude, and P3 latency ($P = 0.259$, $P = 0.328$, $P = 0.552$, respectively).

DISCUSSION

Using event-related brain potentials, we examined cognitive control in an emotional flanker task among non-clinical individuals with LTA, non-clinical individuals with HTA, and patients with GAD. The behavioral results revealed that GAD patients had prolonged response times and increased error rates in emotional flanker task as compared to LTA and HTA individuals. ERPs data demonstrated that in incompatible trials, HTA individuals exhibited a larger N2 amplitude relative to GAD individuals. It was also suggested that HTA and GAD individuals had a smaller P3 amplitude than LTA individuals. Furthermore, CAE contrasts among three study groups showed that LTA individuals owned a better ability in conflict adaptation than the other two groups on N2 amplitude.

High trait anxiety individuals did not reveal prolonged response time and increased behavioral errors, but showed a trend of increased N2 amplitude, reflecting compensatory activation to conflict stimuli. Since a larger N2 amplitude may reflect greater resources being devoted to action monitoring (40, 41), our results suggested that individuals in the HTA group maintained intact work performance with low anxious individuals by recruiting greater cognitive resources and giving more effort. Therefore, our hypothesis that trait anxiety impaired processing efficiency rather than performance effectiveness for individuals with HTA was approved. Similar results were also obtained in the stop-signal task by Savostyanov et al. (42). Greater EEG desynchronization was found in anxious individuals, indicating that more processing effort and resource allocation were required to inhibit a motor response. Coincidentally, ACT argues that in some cases people with high anxiety do not show greater evidence of disrupted attentional control behaviorally, but more cognitive resource was required to perform at a level-standard with low anxious individuals (1, 2). Compared to the LTA group, HTA individuals exhibited weaker P3 components. On account of implications of N2 and P3 components, it was the first time to discover that HTA individuals had a high vigilance to the emotional conflict; however, they showed a deficit in emotion regulatory capability. That is, HTA individuals appeared to have an overactive conflict detection process but poor ability to conflict resolution, which is not inconsistent with our study hypothesis.

By contrast, patients with GAD are associated with deficits in cognitive efficiency with prolonged response times and increased error rates. This is in high agreement with previous studies. For example, in an *N*-back task, Balderston et al. reported that GAD patients showed an overall impairment in both accuracy and reaction time compared to controls (43). Similarly, another empirical study found that clinician-rated anxiety severity predicted slower and less accurate Stroop performance over and above the effect of GAD diagnosis (44). At the neural level, compared to HTA individuals, GAD patients revealed decreased N2 components, while compared to LTA individuals, GAD patients exhibited weaker P3 components. These results suggested that GAD patients could not utilize their limited cognitive resources to achieve the desirable performance outcome. Our results fit better with previous findings that GAD patients showed less activation in the dorsolateral prefrontal cortex, a region critical for cognitive control (43). Therefore, our hypothesis that trait anxiety impaired their processing efficiency and performance effectiveness for GAD patients was proved. Meanwhile, GAD was related to a poor ability to conflict detection and conflict resolution.

Our study found that the cognitive and neural processes implicated in conflict adaptation were altered in the HTA and GAD groups. At the neural level, a significant group difference was found in the index of CAE on N2 amplitude, indicating that the HTA and GAD groups revealed obvious perturbations in emotional conflict adaptation as compared to the LTA group. Furthermore, both the HTA and GAD groups exhibited decreased P3 amplitudes. These results demonstrated that the ability for conflict resolution can be seriously impaired by trait anxiety, thereby resulting in their difficulty in conflict adaptation. It agrees well with a most recent study which found that the P3 amplitude of target stimuli was reduced due to the influence of distraction on anxious individuals (45). This study also corroborates neuroimaging findings by demonstrating that GAD is associated with attenuated response to conflict, which results in impaired top-down control and emotional dysregulation (11).

These results are of great significance for the study of psychiatric diseases. It has been widely assumed that cognitive control studies in subclinical analog samples can be generalized to the corresponding clinical disorder (28). Our findings imply that the pattern of impaired cognitive control, as reported in the high trait anxious sample from normal populations, cannot be directly generalizable to clinical anxiety. We did find significant differences between the HTA and GAD groups. Specifically, different from HTA individuals who had intact performance effectiveness, GAD patients showed impaired cognitive function with prolonged response and poor accuracy in the emotional conflict task. Besides, HTA individuals recruited more cognitive resources to monitor conflict information than GAD patients. Nevertheless, they still have some consistent features in conflict control. Both HTA individuals and GAD patients had impaired processing efficiency and poor abilities to conflict resolution due to their failures in conflict adaptation and decreased P3 amplitudes. These results can deepen and extend our understanding that GAD is associated with a severely impaired cognitive control, while HTA individuals appear to have a moderately impaired cognitive control.

Taken together, the current findings based on clinical and non-clinical individuals shed light on the essential relationship between trait anxiety and cognitive control. In addition, our results distinguish the features of HTA individuals and GAD patients in emotional conflict control. Nevertheless, similar to other studies, our result suffers from a number of limitations. First, the sample size is relatively small, and therefore, it is

insufficient to detect significant among-group differences in conflict adaptation on N2 amplitude. Nevertheless, the magnitude of the trend makes our finding clinically meaningful. These results should be further verified. Second, the results were based on the emotional flanker task. According to a most recent study, anxious individuals preferentially allocate attention to emotional distractors who subsequently exhibit poorer cognitive performance (46). Etkin et al. also asserted that abnormal conflict processing for the clinical patients diagnosed with GAD only manifests in the regulation of emotional conflict, rather than non-emotional conflict (11). Non-emotional flanker task (e.g., arrows) may not elicit impaired cognitive control for the HTA and GAD groups. Therefore, our results need to be replicated and verified in non-emotional flanker stimuli. Third, state anxiety and trait anxiety are highly correlated. According to previous studies, they both have adverse effects on cognitive function (1, 2). However, state anxiety was not assessed in this study. Accordingly, state anxiety and trait anxiety need to be assessed simultaneously in future studies.

Despite these limitations, several key implications can be drawn to better understand the relationship between trait anxiety and conflict control in task. The results in the present study revealed that HTA individuals exhibited comparable performance effectiveness to LTA individuals at the expense of processing efficiency, while GAD patients had shortfalls in both performance effectiveness and processing efficiency. Moreover, HTA individuals revealed poor abilities for conflict resolution rather than for conflict detection, while individuals diagnosed with GAD had impaired conflict detection and conflict resolution functions. Our research provides a powerful support for the viewpoint that trait anxiety can elicit conflict adaptation impairments and suggest that trait anxiety is a predominant factor at the onset of and in the maintenance of GAD. Therefore, trait anxiety reducing strategies may provide significant therapeutic gains.

END NOTES

The following images from the Chinese affective picture system were used in this study in the experimental blocks: angry: AF3, AF5, AF9, AF15, AF23, AM1, AM7, AM20, AM24, and AM33; happy: HF11, HF50, HF115, HF119, HF122, HM10, HM92, HM93, HM94, and HM97.

ETHICS STATEMENT

The study was approved by the institutional review board of Third Military Medical University. The research protocol was carried out in accordance with the recommendations of the principles of Declaration of Helsinki. Written informed consent was obtained from each participant.

AUTHOR CONTRIBUTIONS

YY, LP, BL, and ML designed research; YY, CJ, HX, QY, and WX performed experiments; YY, JL, and YX analyzed data; YY, CJ, FL, and ML wrote and revised the paper.

ACKNOWLEDGMENTS

We sincerely thank Bai L, Ma H, Huang YX, and Luo YJ for providing us with the standardized native Chinese Affective Picture System (CAPS). The photos used in this study were chosen from the CAPS.

FUNDING

This work was supported by National Social Science Foundation of China (Nos. 15CSH056 and 14CSH072), the Projects of Military Research Foundation of the Chinese P.L.A. (Nos. AWS16J025, 3606005, and 14QNP088), and the Advance Research Fund of Third Military Medical University (No. 2016XYY06).

REFERENCES

1. Berggren N, Derakshan N. Attentional control deficits in trait anxiety: why you see them and why you don't. *Biol Psychol* (2013) 92(3):440–6. doi:10.1016/j.biopsycho.2012.03.007
2. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. *Emotion* (2007) 7(2):336–53. doi:10.1037/1528-3542.7.2.336
3. Chen NT, Clarke PJ, Watson TL, MacLeod C, Guastella AJ. Attentional bias modification facilitates attentional control mechanisms: evidence from eye tracking. *Biol Psychol* (2015) 104:139–46. doi:10.1016/j.biopsycho.2014.12.002
4. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophys* (1974) 16(1):143–9. doi:10.3758/BF03203267
5. Fenske MJ, Eastwood JD. Modulation of focused attention by faces expressing emotion: evidence from flanker tasks. *Emotion* (2003) 3(4):327–43. doi:10.1037/1528-3542.3.4.327
6. Egner T, Etkin A, Gale S, Hirsch J. Dissociable neural systems resolve conflict from emotional versus nonemotional distracters. *Cereb Cortex* (2008) 18(6):1475–84. doi:10.1093/cercor/bhm179
7. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* (2006) 51(6):871–82. doi:10.1016/j.neuron.2006.07.029
8. Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD. Conflict monitoring and cognitive control. *Psychol Rev* (2001) 108(3):624–52. doi:10.1037/0033-295X.108.3.624
9. Mansouri FA, Tanaka K, Buckley MJ. Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. *Nat Rev Neurosci* (2009) 10(2):141–52. doi:10.1016/S0040-4039(99)00627-9
10. Purmann S, Badde S, Luna-Rodriguez A, Wendt M. Adaptation to frequent conflict in the Eriksen flanker task: an ERP study. *J Psychophysiol* (2011) 25(2):50–9. doi:10.1027/0269-8803/a000041
11. Etkin A, Prater KE, Hoeft F, Menon V, Schatzberg AF. Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *Am J Psychiatry* (2010) 167(5):545–54. doi:10.1176/appi.ajp.2009.09070931
12. Brydges CR, Fox AM, Reid CL, Anderson M. Predictive validity of the N2 and P3 ERP components to executive functioning in children: a latent-variable analysis. *Front Hum Neurosci* (2014) 8(1):80. doi:10.3389/fnhum.2014.00080
13. Rueda MR, Posner MI, Rothbart MK, Davis-Stober CP. Development of the time course for processing conflict: an event-related potentials study with 4 year olds and adults. *BMC Neurosci* (2014) 5(1):39. doi:10.1186/1471-2202-5-39

14. van Veen V, Carter CS. The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiol Behav* (2002) 77(4–5):477–82. doi:10.1016/S0031-9384(02)00930-7
15. Yeung N, Botvinick MM, Cohen JD. The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol Rev* (2004) 111(4):931–59. doi:10.1037/0033-295X.111.4.931
16. Danielmeier C, Wessel JR, Steinhauser M, Ullsperger M. Modulation of the error-related negativity by response conflict. *Psychophysiology* (2009) 46(6):1288–98. doi:10.1111/j.1469-8986.2009.00860.x
17. Yeung N, Cohen JD. The impact of cognitive deficits on conflict monitoring: predictable dissociations between the error-related negativity and N2. *Psychol Sci* (2006) 17(2):164–71. doi:10.1111/j.1467-9280.2006.01680.x
18. Larson MJ, Clawson A, Clayson PE, Baldwin SA. Cognitive conflict adaptation in generalized anxiety disorder. *Biol Psychol* (2013) 94(2):408–18. doi:10.1016/j.biopsycho.2013.08.006
19. Enriquez-Geppert S, Konrad C, Pantev C, Huster RJ. Conflict and inhibition differentially affect the N200/P300 complex in a combined go/nogo and stop-signal task. *Neuroimage* (2010) 51(2):877–87. doi:10.1016/j.neuroimage.2010.02.043
20. Nicholls C, Bruno R, Matthews A. Chronic *Cannabis* use and ERP correlates of visual selective attention during the performance of a flanker go/nogo task. *Biol Psychol* (2015) 110:115–25. doi:10.1016/j.biopsycho.2015.07.013
21. Hillman CH, Buck SM, Themanson JR, Pontifex MB, Castelli DM. Aerobic fitness and cognitive development: event-related brain potential and task performance indices of executive control in preadolescent children. *Dev Psychol* (2009) 45(1):114–29. doi:10.1037/a0014437
22. Clayson PE, Larson MJ. Conflict adaptation and sequential trial effects: support for the conflict monitoring theory. *Neuropsychologia* (2011) 49(7):1953–61. doi:10.1016/j.neuropsychologia.2011.03.023
23. Groom MJ, Cragg L. Differential modulation of the N2 and P3 event-related potentials by response conflict and inhibition. *Brain Cogn* (2015) 97(Suppl C):1–9. doi:10.1016/j.bandc.2015.04.004
24. Frühholz S, Godde B, Finke M, Herrmann M. Spatio-temporal brain dynamics in a combined stimulus-stimulus and stimulus-response conflict task. *Neuroimage* (2011) 54(1):622–34. doi:10.1016/j.neuroimage.2010.07.071
25. Hughes ME, Fulham WR, Johnston PJ, Michie PT. Stop-signal response inhibition in schizophrenia: behavioural, event-related potential and functional neuroimaging data. *Biol Psychol* (2012) 89(1):220–31. doi:10.1016/j.biopsycho.2011.10.013
26. Wiersema JR, Roeyers H. ERP correlates of effortful control in children with varying levels of ADHD symptoms. *J Abnorm Child Psychol* (2009) 37(3):327–36. doi:10.1007/s10802-008-9288-7
27. Johnstone SJ, Barry RJ, Markovska V, Dimoska A, Clarke AR. Response inhibition and interference control in children with AD/HD: a visual ERP investigation. *Int J Psychophysiol* (2009) 72(2):145–53. doi:10.1016/j.ijpsycho.2008.11.007
28. Yiend J, Mathews A, Burns T, Dutton K, Fernández-Martín A, Georgiou GA, et al. Mechanisms of selective attention in generalized anxiety disorder. *Clin Psychol Sci* (2015) 3(5):758–71. doi:10.1177/2167702614545216
29. Spielberger CD, Gorsuch R, Lushene RE. *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press (1983).
30. Shek DT. The Chinese version of the state-trait anxiety inventory: its relationship to different measures of psychological well-being. *J Clin Psychol* (1993) 49(3):349–58. doi:10.1002/1097-4679(199305)49:3<349:AID-JCLP2270490308>3.0.CO;2-J
31. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psych Meas* (1997) 1(3):385–401. doi:10.1177/014662167700100306
32. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* (1998) 59(Suppl 20):22–33.
33. Si TM, Shu L, Dang WM, Se YA, Chen JX, Dong WT, et al. Evaluation of the reliability and validity of Chinese version of the Mini-International Neuropsychiatric Interview in patients with mental disorders. *Chin Ment Health J* (2009) 23:493–7. doi:10.3969/j.issn.1000-6729.2009.07.011
34. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients – Evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). *J Psychosom Res* (1999) 46(5):437–43. doi:10.1016/S0022-3999(99)00004-5
35. Bai L, Ma H, Huang YX, Luo YJ. The development of native Chinese affective picture system – a pretest in 46 college students. *Chin Ment Health J* (2005) 19(11):719–22. doi:10.3321/j.issn:1000-6729.2005.11.001
36. Nieuwenhuis S, Stins JF, Posthuma D, Polderman T, Boomsma D, de Geus E. Accounting for sequential trial effects in the flanker task: conflict adaptation or associative priming. *Mem Cognit* (2006) 34(6):1260–72. doi:10.3758/BF03193270
37. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* (2004) 134(1):9–21. doi:10.1016/j.jneumeth.2003.10.009
38. Lehmann D, Skrandies W. Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalogr Clin Neurophysiol* (1980) 48(6):609–21. doi:10.1016/0013-4694(80)90419-8
39. Ratcliff R. Methods for dealing with reaction time outliers. *Psychol Bull* (1993) 114(3):510–32. doi:10.1037/0033-2909.114.3.510
40. Dennis TA, Chen CC. Trait anxiety and conflict monitoring following threat: an ERP study. *Psychophysiology* (2009) 46(1):122–31. doi:10.1111/j.1469-8986.2008.00758.x
41. Righi S, Mecacci L, Viggiano MP. Anxiety, cognitive self-evaluation and performance: ERP correlates. *J Anxiety Disord* (2009) 23(8):1132–8. doi:10.1016/j.janxdis.2009.07.018
42. Savostyanov AN, Tsai AC, Liou M, Levin EA, Lee JD, Yurganov AV, et al. EEG-correlates of trait anxiety in the stop-signal paradigm. *Neurosci Lett* (2009) 449(2):112–6. doi:10.1016/j.neulet.2008.10.084
43. Balderston NL, Vytal KE, O'Connell K, Torrisi S, Letkiewicz A, Ernst M, et al. Anxiety patients show reduced working memory related dlPFC activation during safety and threat. *Depress Anxiety* (2017) 34(1):25–36. doi:10.1002/da.22518
44. Hallion LS, Tolin DF, Assaf M, Goethe J, Diefenbach GJ. Cognitive control in generalized anxiety disorder: relation of inhibition impairments to worry and anxiety severity. *Cognitive Ther Res* (2017) 41(4):610–8. doi:10.1007/s10608-017-9832-2
45. Rossi V, Pourtois G. Someone's lurking in the dark: the role of state anxiety on attention deployment to threat-related stimuli. *Biol Psychol* (2017) 122:21–32. doi:10.1016/j.biopsycho.2015.10.014
46. Lichtenstein-Vidne L, Okon-Singer H, Cohen N, Todder D, Aue T, Nemets B, et al. Attentional bias in clinical depression and anxiety: the impact of emotional and non-emotional distracting information. *Biol Psychol* (2017) 122:4–12. doi:10.1016/j.biopsycho.2016.07.012

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RS and handling Editor declared their shared affiliation.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 10 April 2018
doi: 10.3389/fpsyt.2018.00105

Language Patterns Discriminate Mild Depression From Normal Sadness and Euthymic State

Daria Smirnova[1,2], Paul Cumming[3], Elena Sloeva[4], Natalia Kuvshinova[4], Dmitry Romanov[1] and Gennadii Nosachev[1]*

[1] Department of Psychiatry, Addictology, Psychotherapy and Clinical Psychology, Samara State Medical University, Samara, Russia, [2] Centre for Clinical Research in Neuropsychiatry, University of Western Australia, Perth, WA, Australia, [3] School of Psychology and Counselling, Queensland University of Technology, QIMR Berghofer Institute, Brisbane, QLD, Australia, [4] Department of Pedagogy, Psychology and Psycholinguistics, Samara State Medical University, Samara, Russia

OPEN ACCESS

Edited by:
Allan Young, King's College London, United Kingdom

Reviewed by:
Mario F. P. Juruena, South London and Maudsley NHS Foundation Trust, United Kingdom
Rebecca Strawbridge, King's College London, United Kingdom

***Correspondence:**
Daria Smirnova
daria.smirnova.md.phd@gmail.com

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *09 November 2017*
Accepted: *15 March 2018*
Published: *10 April 2018*

Citation:
Smirnova D, Cumming P, Sloeva E, Kuvshinova N, Romanov D and Nosachev G (2018) Language Patterns Discriminate Mild Depression From Normal Sadness and Euthymic State. Front. Psychiatry 9:105. doi: 10.3389/fpsyt.2018.00105

Objectives: Deviations from typical word use have been previously reported in clinical depression, but language patterns of mild depression (MD), as distinct from normal sadness (NS) and euthymic state, are unknown. In this study, we aimed to apply the linguistic approach as an additional diagnostic key for understanding clinical variability along the continuum of affective states.

Methods: We studied 402 written reports from 124 Russian-speaking patients and 77 healthy controls (HC), including 35 cases of NS, using hand-coding procedures. The focus of our psycholinguistic methods was on lexico-semantic [e.g., rhetorical figures (metaphors, similes)], syntactic [e.g., predominant sentence type (single-clause and multi-clause)], and lexico-grammatical [e.g., pronouns (indefinite, personal)] variables. Statistical evaluations included Cohen's kappa for inter-rater reliability measures, a non-parametric approach (Mann–Whitney *U*-test and Pearson chi-square test), one-way ANOVA for between-group differences, Spearman's and point-biserial correlations to analyze relationships between linguistic and gender variables, discriminant analysis (Wilks' λ) of linguistic variables in relation to the affective diagnostic types, all using SPSS-22 (significant, $p < 0.05$).

Results: In MD, as compared with healthy individuals, written responses were longer, demonstrated descriptive rather than analytic style, showed signs of spoken and figurative language, single-clause sentences domination over multi-clause, atypical word order, increased use of personal and indefinite pronouns, and verb use in continuous/imperfective and past tenses. In NS, as compared with HC, we found greater use of lexical repetitions, omission of words, and verbs in continuous and present tenses. MD was significantly differentiated from NS and euthymic state by linguistic variables [98.6%; Wilks' λ(40) = 0.009; $p < 0.001$; $r = 0.992$]. The highest predictors in discrimination between MD, NS, and euthymic state groups were the variables of word order (typical/atypical) ($r = -0.405$), ellipses (omission of words) ($r = 0.583$), colloquialisms (informal words/phrases) ($r = 0.534$), verb tense (past/present/future) ($r = -0.460$), verbs form (continuous/perfect) ($r = 0.345$), amount of reflexive (e.g., myself)/personal ($r = 0.344$), and negative (e.g., nobody)/indefinite ($r = 0.451$) pronouns. The most significant

between-group differences were observed in MD as compared with both NS and euthymic state.

Conclusion: MD is characterized by patterns of atypical language use distinguishing depression from NS and euthymic state, which points to a potential role of linguistic indicators in diagnosing affective states.

Keywords: euthymic state, language patterns, mild depression, negative pronouns, normal sadness, past tense verbs, personal pronouns, word use

INTRODUCTION

Mild depression (MD) is a common mental state (1), observed in 15% of the adult population (2), with only 23% receiving any treatment (3). MD is mostly related to life stresses (4) and [unlike moderate and severe major depressive disorder (MDD)] is poorly responsive to antidepressant medication (1, 5, 6). Nonetheless, MD [as distinct from subthreshold, minor depression (7) or normal sadness (NS) (8, 9)] is a serious medical condition causing professional and personal disabilities (10–12). Indeed, MD is associated with unemployment in 16% of cases (13). The chronic course of mild depressive symptoms within dysthymia brings an elevated suicidality risk, compared with MDD (14). MD is often prodromal to MDD (7, 15, 16). NS in the absence of clinical depression is also frequent (29.8%) in the general population (17).

The ICD-10 (18) diagnosis of MD requires four symptoms, whereas the DSM-V (19) criteria are based on seven main symptoms, and the Hamilton Depression Rating Scale (HDRS) gives an MD diagnosis threshold for scores ranging from 7 to 17 as widely accepted by clinicians or cutoff scores from 8 to 16 as suggested by the recent severity classification of HDRS (20–23). However, depression is heterogeneous and presents with highly variable clinical symptoms, so its diagnosis cannot be made merely by the number of symptoms, but should include their detailed analysis and causal relations (24–26). Diagnosis of MD was reported to be less stable compared with diagnosis of severe depression using ICD-10 criteria and was characterized by a fair level of agreement (kappa = 0.25) between clinicians compared with the moderate reliability in severe depression cases (kappa = 0.53) (8, 27). The claimed high prevalence of MD is sometimes viewed with skepticism, given the questionable reliability of psychiatric diagnoses in general (28), and especially with respect to the differentiation of MD from NS (8, 29). Correct recognition of subthreshold forms of NS is based upon the number, duration, and quality of presented symptoms (30). Despite the elaboration of criteria cited above, psychiatry still lacks objective clinical tests of symptoms comparable with those routinely used in other medical disciplines (31). Affective (e.g., decreased mood) and cognitive (e.g., negative content of thoughts) components of MD and NS are mostly expressed through language, while more severe forms of depression are also recognized by a motor component (e.g., slow bodily movements). The search for objective indicators of MD vs. NS might help to increase the reliability of MD diagnosis. Andreasen and Pfohl (32) first showed that language is a specific marker of depression, and currently active study groups have concluded that an analysis of natural language processing could afford the foundation for developing objective diagnostic tests "based on dimensions of observable behavior" (33) (p. 904).

While a clinical interview remains the basic tool for diagnosing depression (34), linguistic research has demonstrated that systematic analysis of language content reliably classifies patients into appropriate diagnostic groups (35, 36). Nguyen et al. (37) report that computerized word counting techniques (38, 39) discriminate depression communities from other subgroups and also reveal strong online-language predictors of depression (40) and suicide (41). Aberrant written and spoken languages are frequently reported in patients with depression (42–46). Being a chronic affective disorder presenting either within mild depressive symptoms or with marked absence of pleasure in daily activities, dysthymia is characterized by increased speech flow, in contrast to the slowed speech typical of MDD (14). The excessive use of first-person singular pronouns (*I*) correlated with depression in many (22, 23, 38, 46, 47), but not all studies (48). Objective (*me*) and possessive (*my*) first-person pronouns were more frequent in speech of a group with depression, and predicted depression better than did subjective (*I*) pronouns (47). Elevated usage of first-person pronouns was attributed to self-focused attention or self-preoccupation (44, 47, 49). Among various measures of depressive self-focusing style, rumination (repetitions of the same, usually negative, information) has been mentioned in many studies (50–52). Other features of depression included elevated use of mental state verbs (*think*), words denoting causal relations (*because*) (53), greater use of generalizing terms (*everything*, *always*), negation (*nothing*, *never*), and words referring to ambivalent emotional states (54, 55). The increased use of discrepancy words (*should*), possibly reflecting enhanced aspirations for the future (56), has been discussed as a marker of improvement with therapy for depression. Together, these promising results denote that "the styles in which people use words" represent no less meaningful information than "the content of what they say" about their symptoms (38) (p. 548). Nonetheless, language phenomena are still not widely considered for psychiatric diagnosis of affective states.

Hypotheses

Given this background, we predicted that our exploratory analysis of linguistic variables would reveal a set of word-use patterns for differentiation of MD from NS and euthymic state (see Russian/English examples in **Table 1**). *Directional hypotheses.* In accord with previous studies on *lexico-grammatical variables* (42), we predicted that MD patients would (1) make excessive use of first-person/personal and other types of indefinite

TABLE 1 | Linguistic variables included in analysis.[a]

Lexico-semantic variables	
Categorical variables	• Language type: Narration (*description of facts, states, e.g.,* «Стали появляться мысли, что я наношу непоправимый психологический вред моему ребенку и мужу»/*"I started having thoughts that I was causing irreparable psychological damage to my child and husband"*) Reasoning (*assessment, causal relations search, e.g.,* «Я задавал себе вопрос, зачем мне нужно идти туда и не находил ни одного варианта ответа»/*"I was asking myself: why do I have to go there; and couldn't find an answer"*)
Quantitative variables	• Colloquialisms (*informal words/phrases, e.g.,* «не хватает духу»/*"don't have enough spirit"*) • Tautologies (*word and phrases repetitions, e.g.,* «делала это, делала это снова и снова»/*"I was doing it, doing it again and again"*) • Lexical, semantic repetitions (*e.g.,* «плакала и рыдала»/*"I was crying and sobbing"*) • Figurative language/rhetorical figures: Metaphors (*figurative comparison, e.g.,* «погрязла в этом горе»/*"I am drowning in this grief"*) Similes (*direct comparison, e.g.,* «высохла как скелет»/*"I was thin as a skeleton"*)
Syntactic variables	
Categorical variables	• Predominant sentence type: Single-clause (*e.g.,* «Близким от меня одни неприятности»/*"I am just a source of trouble for my family and friends"*) Multi-clause (*e.g.,* «Я не думала, что такой купол на меня опустится»/*"I did not think that such a darkness* (*verbatim, cupola*) *would descend upon me"*) • Single-clause sentence type: Impersonal (*e.g.,* «Дальше только хуже»/*"It only gets worse"*) Reduced (*e.g.,* «Жизнь-болото»/*"Life is a swamp"*) Complete (*e.g.,* «Я просто хотел лежать на диване»/*"I just wanted to lie on the couch"*) Incomplete (*e.g.,* «Хочется не проснуться»/*"Want to not wake up"*) • Multi-clause sentence type: Complex (*absence of causal relations between the clauses' content within one sentence, e.g.,* «В последнее время я думала все чаще, что не нужна никому, никто мной не интересуется»/*"Recently, I have been thinking more and more often, that nobody needs me, nobody cares"*) Compound (presence of causal relations between the clauses' content within one sentence, *e.g.,* «Я постоянно задаю себе вопрос, почему я такой стала»/*"I keep asking myself why I became like this"*) • Word order: Usual/typical (*correct syntax rules, e.g.,* «Я оказалась выброшенной из жизни»/*"I became a throw away from life"*) Unusual/atypical (*e.g.,* «жизнь моя стала тяжелой»/*"a life of mine became difficult"*)
Quantitative variables	• Unusual/atypical word order/rhetorical figures: Ellipses (*omission of words, e.g.,* «он мог делать это, я могла…, тоже»/*"he could do it, I could too"*) Inversions (*unusual/atypical/inverted word order, e.g.,* «никогда не чувствовала я так себя»/*"never I have felt this way before"*)
Lexico-grammatical variables	
Categorical variables	• Person types of pronouns: 1st person singular («я»/*"I"*) or plural («мы»/*"we"*), 2nd person singular («ты»/*"you"*) or plural («Вы»/*"you"*), 3rd person singular («он»/*"he"*) or plural («они»/*"they"*), absence • Verb tenses types: Continuous (*e.g.,* «пыталась»/*"was trying"*), perfect (*e.g.,* «сделала»/*"have done"*) • Verb tenses: Past (*e.g.,* «страдала»/*"was suffering"*), present (*e.g.,* «живу»/*"am living"*), future (*e.g.,* «закончу»/*"will complete"*)
Quantitative variables	• Pronoun types: Indefinite (*e.g.,* «что-либо»/*"anything"*), including Generalized (*e.g.,* «все»/*"everything"*) and Negative (*e.g.,* «никто»/*"nobody"*) Personal (*e.g.,* «я»/*"I"*), including possessive (*e.g.,* «мое»/*"my"*) and reflexive (*e.g.,* «себя»/*"myself"*)

[a]*Examples in Russian and their translation to English are given in brackets.*

(generalized, negative) pronouns, reflecting words of generalization, negation and ambivalent emotional states revealed in depression (54, 55). *Non-directional hypotheses.* Our specific hypotheses follow: Focusing on *syntactic and lexico-semantic variables*, we explored whether MD patients (2) predominantly used single-clause vs. multi-clause sentences and (3) narration vs. reasoning, as reflecting descriptive vs. analytic thought style. We predicted (4) an increased number of lexical (tautologies) and semantic repetitions in MD as a marker of ruminations and depressive self-focusing style (51, 52), and further explored whether MD (5) favors figurative language (metaphors, similes), and (6) unusual/atypical word order related to their emotionally overwhelmed state (54). Based on some previous studies and our own clinical experience, we also hypothesized that, since ruminations are mostly focused on past negative events, MD patients would express *within lexico-grammatical variables* (7) predominantly with the continuous (the imperfective tense of Russian verbs denoting uncompleted actions) rather than the perfect (perfective type/completed actions) form [state-of-being verbs (32)], and (8) the past rather than present or future tense

verbs [past vs. future in depression (57); negative schemas of the past in depression (58)]. Thus, we aimed to apply the linguistic approach as an additional diagnostic key for understanding clinical variability along the continuum of affective states.

MATERIALS AND METHODS

Participants

All 201 subjects gave written informed consent according to the Declaration of Helsinki to participate in the study. The research protocol was approved by the Samara State Medical University's Ethics Committee in 2009. Patients were examined at the University's Department of Psychiatry after referral from general practitioners, neurologists, and psychotherapists, and had not previously consulted a psychiatrist or been prescribed psychotropic medications before or during the brief period of investigation. The diagnoses were based on the results of clinical psychiatric interviews delivered by psychiatrists (Daria Smirnova and Gennadii Nosachev) and were coded using ICD-10 diagnostic criteria. Inclusion criteria for patients were (1) 20–60 years of age; (2) Russian as native language; (3) completion of secondary education; (4) absence of psychiatric comorbidities, as defined in the ICD-10 and examined with a clinical psychiatric interview in the University's Department of Psychiatry, and (5) absence of any overt medical or neurological disorders, based on examination by general practitioners and neurologists upon referral from general practice, or, in the case of patients referred by local psychotherapists, as judged by physicians and neurologists at the University's Psychiatric Hospital. These criteria yielded 124 patients (group MD: 94 females) of mean (SD) age 42 (12) years, coded according to the following ICD-10 categories: (1) F32.0—mild depressive episode (n = 27), (2) F41.2—mixed anxiety and depressive disorder (n = 26), (3) F43.20—adjustment disorder, brief depressive reaction (n = 29), (4) F43.21—adjustment disorder, prolonged depressive reaction (n = 23), or (5) F43.22—adjustment disorder, mixed anxiety, and depressive reaction (n = 19). The mean (SD) length of depressive state in MD cases was 40 (13) days. Most MD had a college or university degree (n = 66; 53%) and lived in an urban area (n = 96; 77%). During clinical interview, patients responded to the question about their life problems or stressors according to the categorization of potential life hazards presented in the rubric Z of ICD-10. The majority of patients (n = 63; 51%) mentioned problems with their primary social group, including family circumstances, 30 (24%), social environment, 22 (18%), employment and unemployment, and 9 (7%), housing and economic circumstances.

Healthy controls (HC), including subgroups of normal healthy (NH) and individuals in a state of NS, were recruited from among volunteers invited by public announcement and signage. Each HC participant was interviewed separately by two psychiatrists (Daria Smirnova and Gennadii Nosachev) of the University's Department of Psychiatry to confirm an absence of history of mental disorders in the past and any present diagnoses based on ICD-10 diagnostic criteria. Qualification of NS state in HC participants was consensus-based (Daria Smirnova and Gennadii Nosachev). Inter-rater reliability on categorization of NH vs. NS between two psychiatrists was high: k = 0.894, $p < 0.001$, 95% CI (0.795–0.993). HC included 77 age- and education-matched native Russian speakers (61 females) of mean (SD) age 40 (12) years. Among HC, 42 participants were designated as NH and 35 were qualified as being in a state of normal sadness (NS), based on reporting current life problems and low mood. The NS individuals were coded as having potential health hazards according to the following ICD-10 categories: Z56—problems related to employment and unemployment (n = 7), Z59—housing and economic circumstances (n = 14), Z60—social environment (n = 4), and Z63—primary support group, including family circumstances (n = 10).

Data Collection Procedures

Clinical psychiatric interviews were used as a database for psychopathological evaluation. In the psycholinguistic approach, we focused on the written self-reports [on the topic (i) "The current state of life and future expectations" and (ii) "The meaning of life"] provided by all participants. The instruction on each of two topics was given orally by a researcher as follows: "Please write as much as you think is necessary and take as much time as you need to describe your current state of life and future expectations." In total, 402 texts were analyzed by the research team, which included a psychiatrist (Daria Smirnova), linguist (Elena Sloeva), and clinical psychologist (Natalia Kuvshinova). While one rater (Daria Smirnova) was necessarily informed about the clinical state of the individuals (patients or HC), the other two raters were blind regarding the group assignment. Both blind raters analyzed the entire sample regarding linguistic variables. The HDRS (21 items) validated Russian version was administered to all subjects. HDRS raters were not blind to MD group, as patients had been referred with the preliminary diagnosis of depression. As for the HC group, HDRS scores have been recorded before the HC (NH vs. NS) group allocation.

Psycholinguistic Analysis

Written samples were analyzed with respect to the number of words in the text using MS Word properties and hand-coding procedures: (i) lexico-semantic [e.g., rhetorical figures (metaphors, similes)], (ii) syntactic [e.g., predominant sentence type (single-clause, multi-clause)], and (iii) lexico-grammatical [e.g., pronouns (indefinite, personal)]. We defined categorical variables according to the participant's predominant usage of each relevant linguistic unit in each linguistic sample. For example, if a participant used 5 single-clause sentences and 10 multi-clause sentences, then the estimate of the variable "Predominant sentence type" was specified as "multi-clause." Quantitative variables were scored as quotients according to the number of the relevant units over a span of 10 sentences. In other words, if a participant used 6 metaphors across 20 sentences, then the quotient of metaphors is equal to 3, calculated as the proportion per 10 sentences. All the variables are summarized in **Table 1**.

Statistical Data Analysis

All data were checked for the assumption of normality using the Shapiro–Wilk test and by inspection of histograms. Differences between study groups were calculated using the non-parametric Mann–Whitney *U*-test, two-tailed, Pearson chi-square test, and one-way ANOVA, depending on the type of variables and number of groups compared. Spearman's bivariate and point-biserial correlations were used to analyze relationships between linguistic data and demographic variable of gender. Values of $p < 0.05$ were considered statistically significant. An inter-rater reliability analysis using the Cohen's kappa statistic was performed to determine consistency between raters on categorization of NH and NS groups and on linguistic variables. Discriminant analysis (Wilks' λ) was used to establish the level of significance in relation to diagnostic types based on linguistic variables. All statistical analyses were performed with the IBM SPSS Statistics 22 (59).

RESULTS

Clinical Description of MD and NS

From the psychiatrist's clinical perspective using the classical approach of descriptive psychopathology, a state of MD was characterized by the following signs and symptoms: (i) depressed mood, consisting of sadness, sorrow, irritability, despondency, or melancholy, (ii) mood swings during the day with predominant hypothymia, and (iii) more prominent mood changes in reaction to current life events. The depressive condition affected the patient's quality of life and was perceived by the patient as a pattern of unwanted or even alien behavioral reactions. Furthermore, MD included partial anhedonia and distortion of self-image to reflect low self-esteem, lack of self-confidence, and self-dislike. Patients also expressed difficulties in decision-making, as well as a pessimistic perception of current life events. Their complaints included a negative view of the past, with emphasis on committed mistakes and failures. Finally, MD was associated with loss of energy, fatigue and lack of interest in social activities. Their somato-autonomic dysfunction manifested in sleep disturbances, changes in appetite, reduced libido, and asthenia.

In contrast to MD, self-perception in the NS subgroup was expressed as an adequate and appropriate reaction to current adverse life events. While NS participants described their emotional experience as a constant subjective feeling of dissatisfaction regarding objective life circumstances arising from external reasons, their ideation was focused on the details of their problematic life situation. The NS group continued their usual daily activities, but with some muting of interests and periods of ruminations accompanied by feelings of sadness. The NS further differed from MD in their focus on present difficulties while analyzing their decision-making and problem-solving strategies, and in that they commonly described future aspirations.

Psychometric Measures

In the MD group, the mean (SD) HDRS-21 total score was 14.3 (2.20), which differed significantly from the NH and NS subgroups: HC-3.03 (0.89), NS-3.77 (0.65), NH-2.40 (0.50), using ANOVA $F(2, 198) = 4{,}110.05$, $p < 0.001$, $\eta^2 = 0.976$, and with significant paired between-groups differences found using *post hoc* Bonferroni correction ($p < 0.05$; $\alpha = 0.05$), $p < 0.001$.

Linguistic Features of MD as Compared with NS and Euthymic State

Mild depression patients produced longer written responses than HC (including NS and NH); the mean (SD) number of words per text was 311 (58) for MD vs. 209 (42) for NS and 197 (29) for HC, $F(107, 93) = 4.17$, $p < 0.001$, effect size $\eta^2 = 0.827$. Written language of MD patients demonstrated distinct peculiarities. The effect sizes were intermediate or large for most differing variables of language (**Tables 2** and **3**). No significant and/or strong correlations were observed between linguistic variables and the factor of gender (all $p > 0.05$). The average inter-rater reliability on linguistic variables between two blind raters was high: $k = 0.840$, $p < 0.001$, 95% CI (0.807–0.865).

Lexico-Semantic Variables

Responses in MD patients, compared with those in HC, were organized more often as narration (MD: 106/124; 85%; HC: 55/77; 71%) and less often as reasoning (MD: 18/124, 15%; HC: 22/77, 29%), $\chi^2(1) = 5.89$, $p = 0.015$, effect size $w = 0.171$, i.e., more often in a descriptive rather than analytic manner. The NH employed more utterances based on reasoning (12/42; 29%) than MD patients (18/124; 15%), $\chi^2(1) = 4.19$, $p = 0.041$, $w = -0.159$.

Mild depression patients used more colloquialisms or informal words/phrases (**Table 2**). Responses in MD also had more repetitions, both with respect to re-using the same words (tautologies) and to expressing the same idea multiple times (lexical and semantic repetitions). The MD group used significantly more metaphors and similes (figurative language) than HC (**Table 2**). In comparison with euthymic NH, the NS group was impoverished at the lexico-semantic sublevel, showing greater use of tautologies and repetitions, in general (**Table 2**).

Syntactic Variables

Ninety nine (80%) MD, compared with only two (2.6%) HC individuals, predominately used single-clause sentences, $\chi^2(1) = 113.37$, $p < 0.001$, $w = 0.751$. Among single-clause sentences, reduced sentences appeared and often predominated in 73% of MD ($n = 91$), compared with 17% of HC cases ($n = 13$), $\chi^2(5) = 141.34$, $p < 0.001$, $w = 0.839$. Among multi-clause sentences, compound sentences were predominately used over complex sentences by the majority of the MD group (106/124, 85%), and more often than in HC (56/77, 73%), $\chi^2(1) = 5.7$, $p = 0.017$, $w = 0.168$. A predominant atypical/inverse word-order usage was also revealed in patients [MD: 124, 100%; HC: 5, 6.5%; $\chi^2(1) = 180.66$, $p < 0.001$, $w = -0.948$]. NS used atypical word-order forms (ellipses and inversions) more often than participants in euthymic state (**Table 2**). There were no significant findings

TABLE 2 | Lexico-semantic and syntactic features in MD, NS, and healthy individuals.

Linguistic variables (quotients)		Descriptive statistics				Between-group comparisons			
	Statistical variables	MD (n = 124)	Control group			MD vs. HC*		MD vs. NH vs. NS*	
			HC (n = 77)	Subgroups		Mann–Whitney U-test		One-way ANOVA	
				NH (n = 42)	NS (n = 35)				
						U	Effect size r	F df (2, 198)	Effect size η^2
Colloquialisms (informal words/phrases)	Mean	3.74	1.21	1.02	1.43	1,675.50	0.631	36.84	0.271
	SD	0.44	0.47	0.15	0.61				
Tautologies (words/lexical repetitions)	Mean	3.77	1.44	1.26	1.66	2,604.00	0.503	7.18	0.067
	SD	0.42	0.50	0.45	0.48				
Lexical and semantic repetitions	Mean	4.42	1.82	1.69	1.97	2,394.00	0.445	30.93	0.238
	SD	0.50	0.39	0.47	0.17				
Rhetorical figures: Ellipses (omission of words)	Mean	1.91	1.53	1.38	1.71	0.00	0.253	518.91	0.409
	SD	0.29	0.53	0.54	0.46				
Inversions (unusual word order)	Mean	4.00	1.08	1.00	1.17	923.50	0.934	104.49	0.839
	SD	0.00	0.27	0.00	0.38				
Metaphors (figurative comparison)	Mean	2.55	1.40	1.48	1.31	3,534.00	0.712	68.62	0.513
	SD	0.84	0.83	0.86	0.80				
Similes (direct comparison)	Mean	1.91	1.53	1.38	1.71	3,449.00	0.261	18.13	0.156
	SD	0.29	0.53	0.54	0.46				

*$p < 0.05$.

HC, the entire healthy control group; NH, normal healthy participants with euthymic state; NS, normal sadness; MD, patients with mild depression.

regarding the preferences in the sentence-type use in NS as compared with either NH or MD.

Lexico-Grammatical Variables

Patients' responses contained significantly more personal and indefinite pronouns, compared with NS and HC (**Table 3**). Data showed greater usage specifically of first-person singular pronouns (e.g., *I*, *me*, *my*) in MD (124/124, 100%) than in HC (55/77, 71%), $\chi^2(3) = 39.78$, $p < 0.001$, $w = 0.445$. MD patients predominately used verbs in continuous tense [MD: 116/124, 94%; HC: 26/77, 34%; $\chi^2(1) = 81.87$, $p < 0.001$, $w = 0.638$] and in past tense [MD: 124/124, 100%; HC: 2/77, 3%; $\chi^2(2) = 192.67$, $p < 0.001$, $w = 0.979$], mostly in first-person singular and impersonal forms [MD: 104/124, 84%; HC: 6/77, 8%; $\chi^2(5) = 69.38$, $p < 0.001$, $w = 0.588$]. While MD used more continuous verbs in the past tense, significantly and with large effect size as shown above, HC used perfect verbs (51/77, 66%) and verbs in the present (51/77, 66%) and future tense (24/77; 32%). Language in NS, compared with NH, included more verbs in continuous form [NS: 19/35, 54%: NH: 7/42, 17%; $\chi^2(1) = 12.08$, $p = 0.001$, $w = 0.396$] and in the present tense [NS: 31/35, 89%; NH: 20/42, 48%; $\chi^2(1) = 20.57$, $p < 0.001$, $w = 0.517$].

Mathematical Modeling of Diagnostic Types of MD, NS, and Euthymic State

Discriminant analysis was performed to establish the level of distinction in linguistic features between investigated study groups. The elements of diagnostic types MD, NS, and NH included lexico-semantic, syntactic, and lexico-grammatical variables, excluding the sentence-type indicators, which did not show significant differences in the between-group analysis for NS (**Table 1**). The model was elaborated using standard SPSS methods to generate a linear equation for calculation of discriminant tabs, as well as validation and refinement of the model's adequacy. Integrated analysis of the discriminant functions revealed the high congruity in classification. 92.5% of original and 89.6% cross-validated grouped cases were correctly classified. The analysis results confirm that our discriminant model significantly characterizes the study sample such that the set of linguistic variables discriminates the states of MD, NS, and euthymic state in NH. The spread of the canonical values in the discriminant model reveals significant differences between MD, NS, and NH [98.6%; test of function 1 through 2: Wilks' $\lambda(40) = 0.009$, $p < 0.001$, canonical correlation $r = 0.992$]. The structure matrix of discriminant analysis demonstrated that the highest significant predictors for

TABLE 3 | Pronouns use in MD, NS, and healthy individuals.

Linguistic variables (quotients)			Descriptive statistics				Between-group comparisons			
		Statistical variables	MD (n = 124)	Control group			MD vs. HC*		MD vs. NH vs. NS*	
				HC (n = 77)	Subgroups		Mann–Whitney U-test		One-way ANOVA	
					NH (n = 42)	NS (n = 35)				
							U	Effect size r	F df (2, 198)	Effect size η^2
Pronouns	Indefinite (e.g., *anything*)	Mean	3.75	1.40	1.29	1.54	129.50	0.916	67.85	0.406
		SD	0.52	0.54	0.46	0.61				
	Generalized (e.g., *everything*)	Mean	3.74	1.58	1.46	1.70	663.50	0.860	4.06	0.039
		SD	0.52	0.60	0.52	0.64				
	Negative (e.g., *nobody*)	Mean	3.75	1.40	1.29	1.54	94.50	0.932	482.81	0.829
		SD	0.51	0.50	0.41	0.60				
	Personal (e.g., *I*)	Mean	3.45	1.83	1.83	1.83	158.00	0.842	235.24	0.704
		SD	0.52	0.52	0.49	0.57				
	Possessive (e.g., *my*)	Mean	3.75	1.58	1.45	1.74	600.00	0.782	153.13	0.607
		SD	0.50	0.61	0.59	0.61				
	Reflexive (e.g., *myself*)	Mean	3.56	1.96	1.90	2.03	1,364.00	0.697	390.95	0.797
		SD	0.54	0.50	0.58	0.38				

*$p < 0.05$.

HC, the entire healthy control group; NH, normal healthy participants with euthymic state; NS, normal sadness; MD, patients with mild depression.

classification of the three groups were the following variables: (i) ellipses ($r = 0.583$), (ii) colloquialisms ($r = 0.534$), (iii) the verb tense ($r = -0.460$), (iv) negative pronouns ($r = 0.451$), (v) word order ($r = -0.405$), (vi) verbs form ($r = 0.345$), and (vii) reflexive pronouns ($r = 0.344$). Based on these data, we repeated the discriminant analysis using only variables with the highest predictability, which yielded similar results [98.3%; test of function 1 through 2: Wilks' $\lambda(14) = 0.015$, $p < 0.001$, $r = 0.987$] (**Figure 1**). As shown in **Figure 1**, MD stands out from NS and NH by function 1, and the centroids for all three groups are significantly different. Collinearity statistical analysis revealed that the variables of verb tense (Tolerance = 0.079, VIF = 12.736) and word order (Tolerance = 0.075, VIF = 13.335) may be responsible for the multicollinearity. However, the discriminant analysis excluding these variables demonstrated highly significant differentiation of diagnostic types MD, NS, and NH based on the remaining language indicators [97.2%; test of function 1 through 2: Wilks' $\lambda(34) = 0.020$, $p < 0.001$, $r = 0.982$]. To specify the contribution of affective component on language use, we also performed another exploratory analysis including the subgroups of MD with and without anxious features, NS, and euthymic state [97.4%; test of function 1 through 3: Wilks' $\lambda(57) = 0.007$, $p < 0.001$, $r = 0.990$] (Data Sheet S1 in Supplementary Material).

DISCUSSION

By choosing the topics for written reports for patients, we intended the diagnostically relevant mental state to appear in the written speech, thus matching responses to the clinical interview and reflecting the context of past and present in the frame of the patients' description of their depressed mood. We assigned the topics about future expectations and meaning of life to document the patients' positive resources, motivations, and potential ability to use the context of the future as reflecting these perspectives for future recovery. However, we concede that these topics might have biased the emotional involvement in patients and thus influenced the content of written reports, as well as the writing style. Our study demonstrated that language of MD patients was characterized by significant differences within the set of lexico-semantic, syntactic, and lexico-grammatical variables, as earlier shown within some language indicators for depression (32, 43, 44, 46). In agreement with a report of increased speech flow in dysthymia, which is mostly characterized by mild depressive symptoms with a chronic course (14), as distinct from the briefer responses in MDD (60), we found longer written responses emerged as a diagnostic sign for discrimination of MD and HC. As predicted, while providing longer responses, our MD patients predominantly used single-clause sentences, reduced utterances, and incomplete phrases with omission of words (ellipses), which reflects the language flow interruptions previously observed in studies of clinical depression (45, 60, 61). We suppose that the pattern of frequent usage of rhetorical figures within phenomena of figurative language (metaphors, similes) and atypical word order (inversions, ellipses) in MD could be interpreted as arising from overt emotional dominance in language content, following the concept presented by Pennebaker et al. (38) about language features reflecting

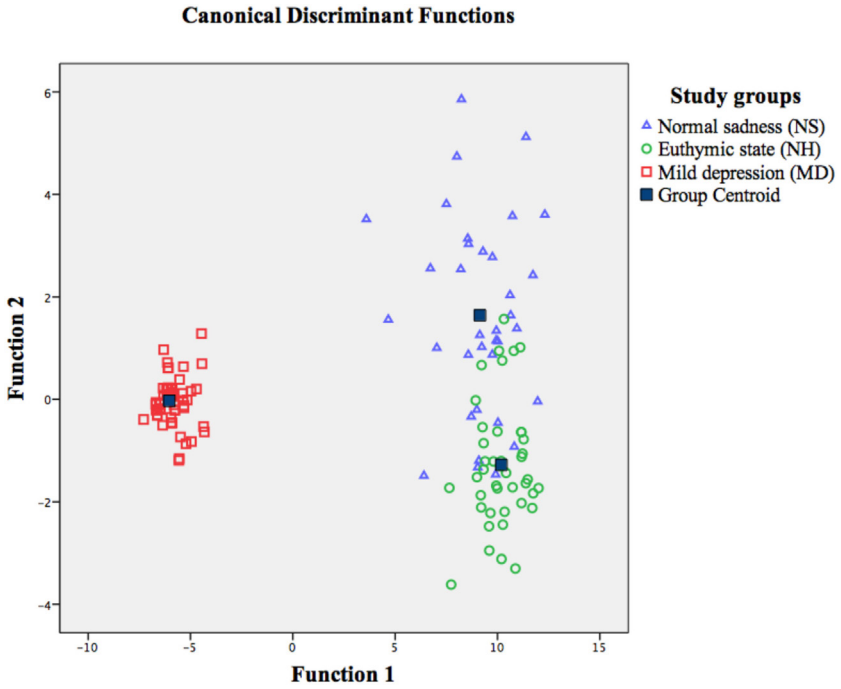

FIGURE 1 | Discriminant model of the diagnostic types of mild depression, normal sadness, and euthymic state in healthy participants, based on linguistic variables (excluding sentence-type analysis).

emotional states and self-perception. According to language development theories (62), figures of speech/rhetorical figures are acquired early in age and their increased use may point to a regression toward earlier forms of language.

Our finding of increased usage of typically oral language expressions (colloquialisms), which was among the highest predictors for differentiation between MD, NS, and NH, together with unusual/atypical word order, confirmed the hypothesized predomination of conversational style over standard written language patterns in MD. Patients seemingly had a certain lack of flexibility, such they could not readily shift from oral conversation with the researcher into the written style appropriate for the self-reporting task. This resembles their difficulty in switching from depressive self-focused attention and ruminations (lexical/word and semantic/topic repetitions) toward potential positive thinking and adaptive coping strategies (50–52).

We also established that, within multi-clause sentences, our MD patients more often used compound sentences (without causal relations between the clauses content with a sentence) than complex sentences (with causal relations between the clauses). This finding in MD stands somewhat in contrast to that of Pennebaker et al. (53), who found generally increased use of causation words (typical for compound-type rather than complex-type multi-clause sentences) in depression, although we did not explicitly rate causation words. In combination with the finding of a predominant use of the single-clause sentences, these properties of sentence use revealed a more frequent addressing to descriptive rather than analytic thought strategies. From a developmental point of view (62), descriptive strategies within narration may represent an early acquired or basal form of verbal behavior, in comparison with the mature analytic style within reasoning acquired later in life. This scenario suggests that MD entails regression in the style of using verbal strategies for organizing the discourse (62). While HC used a mature strategy, including both analysis of events and intellectual reflection (self-analysis and problem-solving behavior), intellectual reflection in MD was subsumed by a sensual/emotional reflection within passive narration.

Consistent with previous findings on greater pronoun use within the context of depressive self-focusing or self-preoccupation style (38, 44, 46, 47, 49, 52), we found that an increased number of personal (e.g., *I*), possessive (e.g., *my*), reflexive (e.g., *myself*) pronouns, gave significant discrimination of MD, NS, and NH. Higher use of personal pronouns was earlier described for healthy participants of female gender (63), but this was not evident in our sample. Enlarged use of generalized (e.g., *everything*) and negative (e.g., *nobody*) indefinite pronouns confirmed previously obtained data describing the overt emotional dominance within generalization, negation, and polarity in emotional expression in depression (54, 55). Frequent use of negative pronouns may refer to the coping mechanisms of denial and negation associated with depressive symptoms or depressive personality traits (44). Insofar as pronouns lack semantic content in their word root, we suggest that their increased use in MD conveys loss of specific meanings in speech and could also be interpreted as a manifestation of semantic impoverishment; this is in keeping with data on reduced semantics in depression (64) and mild cognitive impairment (65).

As we hypothesized, written language in MD was shifted into the past, reflected not only through ruminations about past life events within lexical and semantic repetitions but also in the increased frequency of past tense verbs (57, 58). This concurs with studies demonstrating that depressed patients use fewer discrepancy words (e.g., *should*), which typically symbolize aspirations for the future (56, 66). Our patients used more verbs in continuous/imperfective form, as earlier noted by Andreasen and Pfohl (32). The self-perception of time in MD within the past tense verbs emerged as an additional discriminative feature of the high predictability for differentiation of affective states in our study.

Our findings regarding the patterns of language use as a result of affect or mood influence may reflect not only symptomatic behavior and thinking within the affective states of MD or NS but could also be indicative of stable personality traits or defensive mechanisms, a possibility that requires further investigation (44). However, our discriminant model significantly differentiated the conditions of MD from NS and euthymia with a probability of 98.6%. Another discriminant model using linguistic indicators significantly differentiated the states of MD with and without anxious features, NS and euthymia with the similar level of probability (97.6%). These data may support our hypothesis about the particular effect of affective component on the deviations in language use. This result, which confirms and extends the observations in depression by Oxman et al. (35), Desmet and Hoste (67), Kahn et al. (68), and others, also illuminates the role of assessment of verbal behavior in MD and NS for clarifying the continuum and variety of affective states.

Limitations of the Study and Implications for Further Research

We analyzed only written texts but did not record examples of natural oral speech flow. We used hand-coding procedures and did not apply the Linguistic Inquiry and Word Count (39) computer program elaborated to categorize the text into linguistic categories, because this does not yet exist for Russian language. Also, given the large number of variables examined in the study, we must consider the possible occurrence of type I errors related to interpretation of results. As no patients with psychiatric comorbidities were included, we accordingly isolated the influence of depressive affect on language. As such, we do not take a strong position related to the generalizability of findings in our sample but propose a broader investigation addressing these potential confounds. Future studies might benefit from examining the relationships between language patterns in patients with affective states and their personality traits, thus aiming to define the contribution of personality factors on language use.

We expect that these results will draw more attention to the diagnostic significance of language assessment in psychiatry and clinical disciplines and show that verbal behavior is a sensitive diagnostic marker in MD. We also suggest that this would encourage practitioners to attend not only to *what* the patient utters but also *how* it is spoken. There remains a need for more data regarding linguistic features of conversational language in depression and for generalization to different languages, so as to support a broader applicability of the concept of diagnostic criteria based on written language, and to support precise recommendations for guidelines in clinical practice. In relation to practical implementation, for example, these results might inform the development of a standard questionnaire for diagnosis of MD through written language patterns, designed to be administered by non-experts, and perhaps automatically scored. Present results lead us to contend that linguistic study could inform future clinical approaches to non-pharmacological treatment of MD. Such psychotherapeutic approaches would address not only language content but also language remediation or cognitive training of language style and structure. If symptoms are indeed partially organized by language structure, a treatment approach to normalizing of language might play a beneficial role in improving affective state.

ETHICS STATEMENT

All subjects gave written informed consent according to the Declaration of Helsinki to participate in the study. The research protocol was approved by the Samara State Medical University's Ethics Committee.

AUTHOR CONTRIBUTIONS

DS, GN, and ES designed the project. DS and GN collected the data. DS, GN, ES, and NK analyzed the data with advice from DR and PC. DS, GN, and PC wrote the first draft of the manuscript. All the authors reviewed the final version of the manuscript.

ACKNOWLEDGMENTS

All the authors express the deepest gratitude to Prof. Alexander Krasnov, the Head of Pedagogy, Psychology and Psycholinguistics Department, Samara State Medical University, Samara, Russia, who recently passed away, for his consultation on psycholinguistic issues and strong support of the study. The authors thank their collaborator Prof. Evelina Fedorenko (Massachusetts General Hospital, Harvard Medical School, Department of Psychiatry, MGH/HST Martinos Center for Biomedical Imaging, Harvard, MA, USA) for providing independent expert opinion on the psycholinguistic approach and also for reviewing the manuscript. Their special gratitude goes to Prof. Norman Segalowitz of Concordia University, Montreal, Canada for his detailed review of their manuscript and for suggesting recalculations to highlight the most important findings of the study. The authors wish to express their gratitude to Dr. Maxim Ustinov (Samara State Medical University, Samara, Russia), who assisted in primary statistical evaluations and to all of their patients and healthy volunteers from the control group who participated in the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00105/full#supplementary-material.

REFERENCES

1. Kessler RC, Zhao S, Blazer DG, Swartz M. Prevalence, correlates, and course of minor depression and major depression in the National Comorbidity Survey. *J Affect Disord* (1997) 45:19–30. doi:10.1016/S0165-0327(97)00056-6
2. Shim RS, Baltrus P, Ye J, Rust G. Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005–2008. *J Am Board Fam Med* (2011) 24(1):33–8. doi:10.3122/jabfm.2011.01.100121
3. Wittayanukorn S, Qian J, Hansen RA. Prevalence of depressive symptoms and predictors of treatment among U.S. adults from 2005 to 2010. *Gen Hosp Psychiatry* (2014) 36(3):330–6. doi:10.1016/j.genhosppsych.2013.12.009
4. Kessler R. The effects of stressful life events on depression. *Annu Rev Psychol* (1997) 48:191–214. doi:10.1146/annurev.psych.48.1.191
5. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* (2010) 303(1):47–53. doi:10.1001/jama.2009.1943
6. Barbui C, Cipriani A, Patel V, Ayuso-Mateos J, van Ommeren M. Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. *Br J Psychiatry* (2011) 198(1):11–6. doi:10.1192/bjp.bp.109.076448
7. Meeks T, Vahia I, Lavretsky H, Kulkarni G, Jeste D. A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord* (2011) 129(1):126–42. doi:10.1016/j.jad.2010.09.015
8. Maj M. When does depression become a mental disorder? *Br J Psychiatry* (2011) 199(2):85–6. doi:10.1192/bjp.bp.110.089094
9. Wakefield J, Schmitz M. Severity of complicated versus uncomplicated subthreshold depression: new evidence on the "Monotonicity Thesis" from the national comorbidity survey. *J Affect Disord* (2017) 212:101–9. doi:10.1016/j.jad.2017.01.034
10. Donohue JM, Pincus HA. Reducing the societal burden of depression: a review of economic costs, quality of care and effects of treatment. *Pharmacoeconomics* (2007) 25(1):7–24. doi:10.2165/00019053-200725010-00003
11. Paykel ES, Brugha T, Fryers T. Size and burden of depressive disorders in Europe. *Eur Neuropsychopharmacol* (2005) 15(4):411–23. doi:10.1016/j.euroneuro.2005.04.008
12. World Health Organization. *Depression Fact Sheet No. 369*. World Health Organization (2016). Available from: http://www.who.int/mediacentre/factsheets/fs369/en/ (Accessed: October 17, 2017).
13. Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. *Depress Anxiety* (2010) 27(1):78–89. doi:10.1002/da.20580
14. Holmstrand C, Engström G, Träskman-Bendz L. Disentangling dysthymia from major depressive disorder in suicide attempters' suicidality, comorbidity and symptomatology. *Nord J Psychiatry* (2008) 62(1):25–31. doi:10.1080/08039480801960164
15. Fogel J, Eaton WW, Ford DE. Minor depression as a predictor of the first onset of major depressive disorder over a 15-year follow-up. *Acta Psychiatr Scand* (2006) 113(1):36–43. doi:10.1111/j.1600-0447.2005.00654.x
16. Markkula N, Marola N, Nieminen T, Koskinen S, Saarni S, Härkänen T, et al. Predictors of new-onset depressive disorders – results from the longitudinal Finnish Health 2011 Study. *J Affect Disord* (2017) 208:255–64. doi:10.1016/j.jad.2016.08.051
17. Tebeka S, Pignon B, Amad A, Le Strat Y, Brichant-Petit JC, Thomas P, et al. A study in the general population about sadness to disentangle the continuum from well-being to depressive disorders. *J Affect Disord* (2018) 226:66–71. doi:10.1016/j.jad.2017.08.085
18. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic Criteria for Research*. Geneva: World Health Organisation (1993).
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing (2013).
20. National Collaborating Centre for Mental Health (UK). *Appendix 11, The Classification of Depression and Depression Rating Scales/Questionnaires. Depression: The Treatment and Management of Depression in Adults (Updated Edition)*. Leicester, UK: British Psychological Society (2010). NICE Clinical Guidelines, No. 90. Available from: https://www.ncbi.nlm.nih.gov/books/NBK63740/
21. Cusin C, Yang H, Yeung A, Fava M. Rating scales for depression. In: Baer L, Blais MA, editors. *Handbook of Clinical Rating Scales and Assessment in Psychiatry and Mental Health*. New York: Humana Press (2010). p. 7–35.
22. Zimmerman J, Wolf M, Bock A, Peham D, Benecke C. The way we refer to ourselves reflects how we relate to others: associations between first-person pronoun use and interpersonal problems. *J Res Pers* (2013) 47(3):218–25. doi:10.1016/j.jrp.2013.01.008
23. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord* (2013) 150(2):384–8. doi:10.1016/j.jad.2013.04.028
24. Goldberg D. The heterogeneity of "major depression". *World Psychiatry* (2011) 10:226–8. doi:10.1002/j.2051-5545.2011.tb00061.x
25. Fried EI, Nesse RM. Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. *BMC Med* (2015) 13:72. doi:10.1186/s12916-015-0325-4
26. Kessing LV, Bukh JD. The clinical relevance of qualitatively distinct subtypes of depression. *World Psychiatry* (2017) 16(3):318–9. doi:10.1002/wps.20461
27. Kessing LV. Severity of depressive episodes according to ICD-10: prediction of risk of relapse and suicide. *Br J Psychiatry* (2004) 184:153–6. doi:10.1192/bjp.184.2.153
28. Faravelli C, Castellini G, Landi M, Brugnera A. Are psychiatric diagnoses an obstacle for research and practice? Reliability, validity and the problem of psychiatric diagnoses. The case of GAD. *Clin Pract Epidemiol Ment Health* (2012) 8:12–5. doi:10.2174/1745017901208010012
29. Horwitz AV, Wakefield JC. *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Depressive Disorder*. New York: Oxford University Press (2007). 312 p.
30. Andrews G, Anderson TM, Slad T, Sunderland M. Classification of anxiety and depressive disorders: problems and solutions. *Depress Anxiety* (2008) 25:274–81. doi:10.1002/da.20489
31. Bedi G, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB, et al. Automated analysis of free speech predicts psychosis onset in high-risk youths. *NPJ Schizophr* (2015) 1:15030. doi:10.1038/npjschz.2015.30
32. Andreasen NG, Pfohl B. Linguistic analysis of speech in affective disorders. *Arch Gen Psychiatry* (1976) 33(11):1361–7. doi:10.1001/archpsyc.1976.01770110089009
33. Elvevåg B, Cohen AS, Wolters MK, Whalley HC, Gountouna V-E, Kuznetsova KA, et al. An examination of the language construct in NIMH's research domain criteria: time for reconceptualization! *Am J Med Genet B Neuropsychiatr Genet* (2016) 171(6):904–19. doi:10.1002/ajmg.b.32438
34. Lopez-Ibor JJ. Clinical interview as the basic tool for the diagnosis of depression. *WPA Bull Depress* (1993) 1(1):7.
35. Oxman TE, Rosenberg SD, Schnurr PP, Tucker GJ. Diagnostic classification through content analysis of patients' speech. *Am J Psychiatry* (1988) 145(4):464–8. doi:10.1176/ajp.145.4.464
36. Tausczik YR, Pennebaker JW. The psychological meaning of words: LIWC and computerized text analysis methods. *J Lang Soc Psychol* (2010) 29(1):24–54. doi:10.1177/0261927X09351676
37. Nguyen T, O'Dea B, Larsen M, Phung D, Venkatesh S, Christensen H. Using linguistic and topic analysis to classify sub-groups of online depression communities. *Multimed Tools Appl* (2015) 1:24. doi:10.1007/s11042-015-3128-x
38. Pennebaker JW, Mehl MR, Niederhoffer KG. Psychological aspects of natural language use: our words, our selves. *Annu Rev Psychol* (2003) 54:547–77. doi:10.1146/annurev.psych.54.101601.145041
39. Pennebaker JW, Francis ME, Booth RJ. *Linguistic Inquiry and Word Count (LIWC)*. Austin, Texas (2007). Available from: liwc.net (Accessed: October 20, 2017).
40. Ramirez-Esparza N, Chung CK, Kacewicz E, Pennebaker JW. The psychology of word use in depression forums in English and in Spanish: testing two text analytic approaches. *Proceedings of AAAI International Conference on Weblogs and Social Media*. Seattle, Washington (2008). p. 102–8.
41. Stirman SW, Pennebaker JW. Word use in the poetry of suicidal and non-suicidal poets. *Psychosom Med* (2001) 63(4):517–22. doi:10.1097/00006842-200107000-00001

42. Rude SS, Gortner E-M, Pennebaker JW. Language use of depressed and depression-vulnerable college students. *Cogn Emot* (2004) 18(8):1121–33. doi:10.1080/02699930441000030
43. Bucci W, Freedman N. The language of depression. *Bull Menninger Clin* (1981) 45:334–58.
44. Weintraub W. *Verbal Behavior: Adaptation and Psychopathology*. New York: Springer (1981). 214 p.
45. Breznitz Z. Verbal indicators of depression. *J Gen Psychol* (1992) 119(4): 351–63. doi:10.1080/00221309.1992.9921178
46. Bernard JD, Baddeley JL, Rodriguez BF, Burke PA. Depression, language, and affect: an examination of the influence of baseline depression and affect induction on language. *J Lang Soc Psychol* (2016) 35(3):317–26. doi:10.1177/0261927X15589186
47. Zimmerman J, Brockmeyer T, Hunn M, Schauenburg H, Wolf M. First-person pronoun use in spoken language as a predictor of future depressive symptoms: preliminary evidence from a clinical sample of depressed patients. *Clin Psychol Psychother* (2017) 24(2):384–91. doi:10.1002/cpp.2006
48. Brockmeyer T, Zimmermann J, Kulessa D, Hautzinger M, Bents H, Friederich H-C, et al. Me, myself, and I: self-referent word use as an indicator of self-focused attention and its link to depression and anxiety. *Front Psychol* (2015) 6:1564. doi:10.3389/fpsyg.2015.01564
49. Pyszczynski T, Greenberg J. Self-regulatory perseveration and the depressive self-focusing style: a self-awareness theory of reactive depression. *Psychol Bull* (1987) 102(1):122–38. doi:10.1037/0033-2909.102.1.122
50. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion regulation strategies across psychopathology: a meta-analytic review. *Clin Psychol Rev* (2010) 30(2):217–37. doi:10.1016/j.cpr.2009.11.004
51. Mor N, Winquist J. Self-focused attention and negative affect: a meta-analysis. *Psychol Bull* (2002) 128:638–62. doi:10.1037/0033-2909.128.4.638
52. Watkins E, Brown RG. Rumination and executive function in depression: an experimental study. *J Neurol Neurosurg Psychiatry* (2002) 72(3):400–2. doi:10.1136/jnnp.72.3.400
53. Pennebaker JW, Mayne TJ, Francis ME. Linguistic predictors of adaptive bereavement. *J Pers Soc Psychol* (1997) 72(4):863–71. doi:10.1037/0022-3514.72.4.863
54. Gawda B. The analysis of farewell letters of suicidal persons. *Bull Soc Sci Med Grand Duche Luxemb* (2008) 1:67–74.
55. Pusztai A, Bugán A. Analysis of suicide notes form persons committing completed suicides. *Psychiatr Hung* (2005) 20(4):271–80.
56. Van der Zanden R, Curie K, Van Londen M, Kramer J, Steen G, Cuijpers P. Web-based depression treatment: associations of clients' word use with adherence and outcome. *J Affect Disord* (2014) 160:10–3. doi:10.1016/j.jad.2014.01.005
57. Eysenck M, Payne S, Santos R. Anxiety and depression: past, present, and future events. *Cogn Emot* (2006) 20(2):274–94. doi:10.1080/02699930500220066
58. Gross J, Blank H, Bayen UJ. Hindsight bias in depression. *Clin Psychol Sci* (2017) 5(5):771–88. doi:10.1177/2167702617712262
59. IBM Corp. *IBM SPSS Statistics for Mac, Version 22.0*. Armonk, NY: IBM Corp (2012).
60. Krasnov VN. Affective disorders. In: Dmitrieva TB, Krasnov VN, Neznanov NG, Semke VY, Tiganov AS, editors. *Psychiatry. National Guidelines*. Moscow: GEOTAR (2009). p. 490–525.
61. Pope B, Blass T, Siegman AW, Raher J. Anxiety and depression in speech. *J Consult Clin Psychol* (1970) 35(1):128–33. doi:10.1037/h0029659
62. Locke JL. A theory of neurolinguistic development. *Brain Lang* (1997) 58(2):265–326. doi:10.1006/brln.1997.1791
63. Pennebaker JW, King L. Linguistic styles: language use as an individual difference. *J Pers Soc Psychol* (1999) 77:1296–312. doi:10.1037/0022-3514.77.6.1296
64. Fossati P, Guillaume le B, Ergis AM, Allilaire JF. Qualitative analysis of verbal fluency in depression. *Psychiatry Res* (2003) 117(1):17–24. doi:10.1016/S0165-1781(02)00300-1
65. Roark B, Mitchell M, Hosom J-P, Hollingshead K, Kaye J. Spoken language derived measures for detecting mild cognitive impairment. *IEEE Trans Audio Speech Lang Processing* (2011) 19(7):2081–90. doi:10.1109/TASL.2011.2112351
66. Ravdin LD, Katzen HL, Agrawal P, Relkin NR. Letter and semantic fluency in older adults: effects of mild depressive symptoms and age-stratified normative data. *Clin Neuropsychol* (2003) 17(2):195–202. doi:10.1076/clin.17.2.195.16500
67. Desmet B, Hoste V. Combining lexico-semantic features for emotion classification in suicide notes. *Biomed Inform Insights* (2012) 5(1):125–8. doi:10.4137/BII.S8960
68. Kahn JH, Tobin RM, Massey AE, Anderson JA. Measuring emotional expression with the Linguistic Inquiry and Word Count. *Am J Psychol* (2007) 120(2):263–86.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RS and handling editor declared their shared affiliation.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 04 July 2018
doi: 10.3389/fpsyt.2018.00296

Regional Cerebral Blood Flow in *Mania: Assessment Using 320-Slice Computed* Tomography

Yiming Wang[1,2,3], Xingde Liu[4]*, Peifan Li[1], Haiyan Zhou[5], Lixia Yang[1], Lei Zheng[1], Pingxia Xie[1], Lingjiang Li[6], D. Joshua Liao[7], Qianqian Liu[1] and Deyu Fang[8]*

[1] Department of Psychiatry, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [2] Neuroelectrophysiological Testing Center, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [3] College Students' Mental Health Education and Counseling Center, Guizhou Medical University, Guiyang, China, [4] Department of Cardiology, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [5] Clinical Research Center, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [6] The Second Xiangya Hospital, Central South University, Changsha, China, [7] Department of Pathology, Affiliated Hospital of Guizhou Medical University, Guiyang, China, [8] Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

OPEN ACCESS

Edited by:
Catherine Harmer, Warneford Hospital, United Kingdom

Reviewed by:
Martin Schäfer, Kliniken Essen-Mitte, Germany
Mitul Ashok Mehta, King's College London, United Kingdom
Richard Porter, University of Otago, New Zealand

***Correspondence:**
Yiming Wang
yimingwang@gmc.edu.cn
Xingde Liu
lxd@gmc.edu.cn

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *19 February 2018*
Accepted: *15 June 2018*
Published: *04 July 2018*

Citation:
Wang Y, Liu X, Li P, Zhou H, Yang L, Zheng L, Xie P, Li L, Liao DJ, Liu Q and Fang D (2018) Regional Cerebral Blood Flow in Mania: Assessment Using 320-Slice Computed Tomography. Front. Psychiatry 9:296. doi: 10.3389/fpsyt.2018.00296

Objectives: While evidence that episodes of mania in bipolar I are associated with changes in bioenergetic and regional cerebral blood flow (rCBF) and cerebral blood flow velocity (rCBFV), both the regions and the extent of these changes have not yet been defined. Therefore, we determined the pattern of regional cerebral perfusion mania patients and using patients with major depressive disorder (MDD) as positive controls and healthy participants as negative controls.

Methods: Twenty participants with mania, together with 22 MDD patients and 24 healthy volunteers, were recruited for this study. On all participants, Transcranial Doppler (TCD) was conducted to measure rCBFV parameters, 320-slice CT was conducted to measure rCBF in the different cerebral artery regions, and hematological parameters were assessed. ANOVA and Pearson's tests were used for the statistical analysis.

Results: Our data indicated that rCBF in the medial temporal lobe and hippocampus, especially in the left medial temporal lobe and the right hippocampus, was increased in the mania group compared with the control and MDD groups ($p < 0.01$). In contrast, rCBF in the medial temporal lobe and hippocampus was decreased in the depression group ($p < 0.01$) compared with healthy controls. In addition, values of rCBFV in the bilateral internal carotid arteries (ICAs) and middle cerebral arteries (MCA) were increased in mania ($p < 0.01$) in comparison to the MDD group. Whole blood viscosity and hematocrit as well as red blood cell sedimentation rate remained unchanged in all group ($p > 0.05$).

Conclusions: In mania, rCBF is increased in the medial temporal lobe and hippocampus, with a corresponding increase in rCBFV in the same regions.

Keywords: mania bipolar disorder, depression, transcranial doppler ultrasound, 320-slice CT, mitochondria, energy, blood flow

INTRODUCTION

Symptomatically, mania in bipolar disorder is characterized by increased energy (1). Conversely depression in bipolar disorder is associated with decreased energy (2). There is evidence showing increased resting energy expenditure in manic episode patients, suggesting an altered regulation of energy and local cerebral blood flow in mania (3). Takeda et al. have observed that the brain advanced function is related to the changes in the cerebral blood flow perfusion, and that both cerebral blood flow and blood flow velocity in certain regions will change when human emotion is changed (4). However, more work is required to better understand the cerebral blood flow involved in bipolar disorder.

In vivo neuroimaging studies can assist in understanding the neural regions involved in energy dysfunction in bipolar disorder via analyzing blood flow and metabolic processes. A meta-analysis of comprising 65 functional magnetic resonance imaging (fMRI) studies of 1,074 healthy volunteers and 1,040 bipolar disorder cases, showed abnormal inferior frontal cortex and medial temporal activation in bipolar disorder, especially, in mania, inferior frontal cortex under activation has been observed to relate to both emotional and cognitive processing (5). A other study using positron emission tomography (PET) suggests decreased activity in the anterior cingulated and caudate using positron emission tomography (6). Studies of whole-brain PET imaging examining glucose utilization have shown increases in mania and decreases in depression (7). A recent study with magnetic resonance spectroscopy (MRS) reports that euthymic bipolar disorder subjects fail to replenish ATP from phosphocreatine through creatine kinase (CK) enzyme catalysis during tissue activation in the occipital lobe (8). A novel MRI method sensitive to proton chemical exchange (affected by pH, metabolite concentration, and cellular density) has been used to study subjects with euthymic bipolar disorder vs. controls (9), where consistent metabolic and structural abnormalities in bipolar disorder particularly in cerebral white matter and the cerebellum are discerned. However, other studies using single photon emission computerized tomography (SPECT) report that in comparison to controls, subjects with mania manifest significantly reduced perfusion in many regions, including the left frontal area, left anterior cingulate and parietal cortices (10). Patients with unipolar depression have significantly lowered perfusion than controls in most of the regions examined, mainly in the anterior temporal and frontal cortices bilaterally; they also have lowered perfusion in the right anterior temporal and frontal areas, as well as the right middle temporal area and the right thalamus, compared with manic patients (11).

At present, more and more techniques, including SPECT, positron emission tomography (PECT), TCD, MRI, etc., have been used for cerebral blood flow research. The above-mentioned studies on cerebral blood flow in bipolar disorder are inconsistented, and this methods are just semi-quantitative measurement. The results are just ratio, rather than absolute value of cerebral blood flow. TCD is convenient and easy to do, but it just is a qualitative indicator (12). The PECT image acquisition time is long and difficult to obtain (13). MR perfusion is only used on MR machines with planar echo techniques and cannot be used extensively (14). Since the 320-slice CT was applied to the clinic, whole brain perfusion imaging technology has been successfully applied to the study of cerebrovascular diseases (15). Although both employ the same principle of perfusion imaging, compared with traditional CT, 320-slice CT can extend the original narrow coverage to 160mm, can obtain the whole brain volume data one-time, and can quickly, accurately and stereoscopically measure cerebral blood flow (16). 320-slice CT is more comprehensive for diagnosis and study of cerebrovascular diseases.

In this study, monitoring rCBF using the novel imaging technique our goal was to clarify the pattern of regional cerebral perfusion in cerebral hemispheres of mania with bipolar I disorder that offers quantitative and high-resolution cerebral perfusion analyses, also furthermore in order to clarify its potential utility to psychiatric disorder for possible diagnostic and treatment response purposes.

Specifically, we aimed to compare rCBF in bipolar I disorder to both MDD subjects and healthy individuals as controls to clarify regional cerebral perfusion patterns in the different cerebral areas. The main method employed was the Toshiba Aquilion ONE 320 slice dynamic volume Computed-Tomography (320 slice CT) whole brain one-stop scanning, in combination with Transcranial Doppler (TCD) ultrasound and hematological parameters, to assess rCBF and cerebral blood flow velocity (rCBFV) and blood viscosity. Our novel use of this technique in a study on depression has been outlined recently (17).

MATERIALS AND METHODS

Subjects

Twenty patients with the manic phase of bipolar I disorder were selected for the study. They were either hospitalized patients or outpatients with episodes of mania in the Psychiatry Department of Guizhou Medical University Hospital, GuiHang 300 Hospital or the Second People's Hospital of Guizhou Province, from July of 2014 to May of 2016. All examinations were performed before the patients received drug treatment, and all patients did not take antipsychotics for a month before they were hospitalized. All the patients met diagnostic criteria for a manic episode of bipolar I disorder as defined by DSM-IV-TR (Elevated, exaggerated, or irritated mood continues for at least one week, or less, but scratching the extent of hospitalization. At the same time, patients have exaggerated self-evaluation, reduced sleep, more volubility, drifted idea, and so on. These symptoms do not meet the criteria for mixed seizures and are not due to substance or the direct physiological effects, but can result in obvious defects in professional, daily social activities, interpersonal relationships) (diagnosed by two clinicians), a Bech-Rafaelsen Manic Rating scale (BRMS13) >14 (mean, 35.25 ± 10.12), a Hamilton Depression Rating Scale (HAMD24) <8 scores, and a Self-Rating Depression Scale (SDS) <50 scores. The diagnosis criteria for the MDD group ($n = 22$) met with a Hamilton Depression Rating Scale 24 (HAMD24) score of >20 points. A SDS score >53 were used in this study.

Exclusion criteria for all groups included, (i) no history for taking drugs that could influence vessel compliance function upon enrollment (such as stimulants, hypnotics or sedatives) within 6 months, (ii) no other diseases of the nervous system, in particular aneurysms involving the supra-aortic vessels and chronic cerebral venous insufficiency, (iii) no active somatic diseases (e.g., diabetes, hypertension, coronary heart disease, and atherosclerosis) and (iv) no other significant mental disorders.

Twenty-four healthy volunteers, age and gender matched, with a HAMD24 score <20 and without any histories of bipolar I disorder, depression or significant somatic disorders were selected as normal controls. The physical examinations of these healthy controls were performed in the physical examination center of Guizhou Medical University Hospital.

Ethics Statement and Consent

The study was approved by the Ethics of Human Investigation Committee of Guizhou Medical University (NO: 20140016) and all procedures were conducted in accordance with relevant guidelines and regulations as well as with the updated Declaration of Helsinki (18). The participants themselves or legally authorized representatives had signed a written informed consent and obtained safeguards in this study.

Hemorheologic Measurement

Venous blood (3 ml) was collected in the morning (08:00–09:00) from each participant, with heparin as an anticoagulant, and used for analyses of blood viscosity (including high middle low shear rates), hemoconcentration, hematocrit (HCT) and red blood cell sedimentation with an instrument named automatic blood rheometer (LBY-N6B, Beijing Precil Instrument Co. Ltd.).

Transcranial Doppler Screening Method

Each subject was assessed using the 2 MHz probe transcranial color-coded Doppler (TCD) sonography (Germany, DWL-X type), in accordance with the guideline of Hua-Yang TCD ultrasound practice and with the diagnostic criteria (19), at 9:00 am on an empty stomach in a quiescent condition. The mean flow velocity (Vm), systolic peak velocity (Vs), diastolic velocity (Vd) in the middle cerebral artery (MCA), anterior cerebral artery (ACA), and inferior cerebral artery (ICA) were detected through different bone windows as we described previously (17). The Pulsatility Index (PI) was calculated as PI = (peak systolic velocity end diastolic velocity)/mean blood flow velocity. Data was generated by the TCD analysis software *via* the trace envelope of the measured arterial spectrum and a series of blood flow parameter values.

Regional Cerebral Blood Flow Measurement and Perfusion Image Analysis Methods

After collection of clinical and demographic data, subjects were studied using TCD screening. All subjects were measured for rCBF in the different cerebral artery regions using the 320 slice CT (20) (Japan's Toshiba Aquilion ONE, non-helical scan mode, 912-channel, 16 cm coverage, lap rotation time 0.5 s, slice thickness 0.5 mm, vision 240 mm). Assessment was done at 10:00 am on an empty stomach with the method described previously (17). The area of interest was selected on the whole brain perfusion image to measure regional cerebral blood flow (rCBF). These interests are in line with the following requirements: (1) Located between the Reid baseline cross-section and the paracentral lobule cross-section. (2) Located in the frontal lobe, temporal lobe, basal ganglia, and hippocampus. (3) The size of the region of interest is 1 cm2. (4) The blood flow in the area is greatly affected by the emotional state. (5) Avoid large blood vessels. (6) Symmetrical selection. (7) The same position is selected for each patient.

Statistical Analyses

Data were analyzed using SPSS Version 22.0 and presented as means ± SEM. Chi-square of independent samples and one way ANOVA were used to determine the significant difference among groups with $P < 0.05$ considered significant. Dunnett-t was used to multiple comparisons. A series of Pearson's correlations were carried out to determine the strength and the relationship between rCBF and rCBFV parameters, with 95% confidence intervals used. Multiple linear regression was conducted to analyze these factors (including age, mania and depression) that influence rCBF and rCBFV. Simple randomization was conducted using SAS version 9.1.

RESULTS

Clinical Features

All participants were selected with both age and gender matched. Therefore, there were no significant difference among the bipolar I disorder, MDD and control groups observed for demographic variables in age (mania group: 19–60 years old mean 32.74 ± 14.27 years old; control group: 19–60 years old, mean 42.29 ± 9.54; and depression group: 19–60 years old, mean 39.86 ± 14.25) and other parameters (including sex, blood pressure, smoking, and hypertension), as shown in **Table 1**. In addition, hematological parameters, including blood viscosity (high middle low shear rate), hematocrit and red blood cell sedimentation, did not show significant differences between the depression and control groups (**Table 2**).

Comparisons of rCBF Among the Mania, Depression, and Control Groups

Compared with the control and the depression groups, rCBF in the medial temporal lobe and hippocampus was all increased in manic patients ($P < 0.005$). In contrast, rCBF in the medial temporal lobe and hippocampus was reduced in the MDD group compared with the healthy controls ($P < 0.05$) (**Figure 1D**, photo **Figures 1A–C**, left: temporal lobe, right: hippocampus). Notably from **Figure 1E**, rCBF in the left medial temporal lobe and right hippocampus was much higher in the mania group than in the depression group ($P < 0.05$).

Comparisons of rCBFV Among the Mania, Depression, and Control Groups

Compared with the control and depression groups, the values of Vs, Vd, and Vm of rCBFV in the left ICA and MCA were

TABLE 1 | Comparisons of demographic variables amongdifferent groups.

Factors	Groups	Mania ($n = 20$)	Control ($n = 24$)	Depression ($n = 22$)	F/X2	*P*-value
Age		32.74 ± 14.27	42.29 ± 9.54	39.86 ± 14.25	3.156	0.052
Sex	M	8 (40%)	10 (41%)	8 (36.4%)	2.825	0.086
	F	12 (60%)	14 (59%)	14 (63.6%)		
Smoking	Yes	4 (20%)	6 (25%)	5 (22.7%)	1.375	0.548
	No	16 (80%)	18 (75%)	17 (77.3%)		
Alcohol drinking	Yes	17 (85%)	20 (83.3%)	16 (72.7%)	1.394	0.532
	No	3 (15%)	4 (16.7%)	6 (27.3%)		
Hypertension(>140/90 mmHg)	Yes	4 (20%)	5 (20.8%)	7 (31.8%)	1.524	0.439
	No	16 (80%)	19 (79.2%)	15 (68.2%)		

TABLE 2 | Comparisons of hematological parameters among the mania, normal and depression groups ($\bar{x} \pm s$).

Items	Mania ($n = 20$)	Control ($n = 24$)	Depression ($n = 22$)	*P*-value
High shear rate (mPa.s/150S 21)	4.44 ± 0.61	4.53 ± 0.45	4.21 ± 0.50	0.900
Middle shear rate (mPa.s/60S 21)	5.32 ± 0.72	5.36 ± 0.58	5.04 ± 0.60	0.925
Low shear rate (mPa.s/10S 21)	9.35 ± 1.92	8.71 ± 1.23	8.32 ± 1.40	0.901
Hematocrit	0.46 ± 0.04	0.45 ± 0.03	0.45 ± 0.03	0.971
Red blood cell sedi -mentation (mm/h)	28.17 ± 11.61	35.39 ± 5.54	34.47 ± 7.35	0.803

increased in the mania group, and the Vs and Vm values in the right ICA and MCA ($P < 0.05$). In contrast, the values of Vs, Vd, and Vm of rCBFV in the left ICA and left MCA were decreased in the depression group, and the Vs and Vm values in the right MCA and the right ICA, compared with the control group ($P < 0.05$). However, no significant differences were discerned in values of PI and RI of rCBFV in the ICA and MCA among all three studied groups (**Figures 2A,B**).

Relationship Between rCBF and rCBFV in Mania

There was a positive correlation between rCBFV and rCBF in the left medial temporal lobe and the right hippocampus in the mania group, such that there was a positive relationship between rCBFV (including MCA-L-Vs, MCA-L-Vd, MCA-L-Vm, MCA-R-Vs, MCA-R-Vd, MCA-R-Vm, ICA-L-Vs, ICA-L-Vd, ICA-L-Vm, ICA-R-Vs, ICA-R-Vd, and ICA-R-Vm) and rCBF in the medial temporal lobe and the hippocampus in the mania group ($r = 0.815$, $P < 0.05$) (**Figures 3A,B**).

The Effects of Mania, Depression, and Age on rCBF and rCBFV

We found that age and depression had negative effects on rCBF in the medial temporal lobe and hippocampus, and rCBFV in MCA and ICA, while manic had positive effects on rCBF in the medial temporal lobe and hippocampus, and rCBFV in MCA and ICA. In particular, both manic and depression can still affected rCBF in the medial temporal lobe and hippocampus, and rCBFV in MCA and ICA after the exclusion of age (**Tables 3**, **4**) ($R = 0.376$, $P < 0.05$).

DISCUSSION

Using 320 slice CT imaging to measure rCBF and rCBFV in MDD, as articulated in our previous study (17), is novel in psychiatry study and leads to the observations that rCBFV is positively correlated with the corresponding vascular rCBF in both gray and white matters, that prominent changes occur in grey matter blood flow, and that rCBF of the left gray matter is lower than its right counterpart in MDD. In this study, we use this approach for the first time in study of mania in bipolar I and obtain intriguing data.

Available information regarding perfusion and metabolic activity in mania is quite controversial. Some studies show increases in various brain regions (3, 21) while some others show decreases (5, 8–10). Deckersbach observed increased rCBF in the left dorsolateral prefrontal cortex in patients with bipolar disorder, also associated with episodic memory and learning (22). However, another study not only indicated significantly reduced perfusion in the left frontal, anterior cingulate and parietal cortices areas in mania patients but also showed a close correlation between the severity of psychotic symptoms and reduced rCBF (10). Hyper-perfusion of frontal and temporal lobes was detected in patients with bipolar disorder, potentially indicative of over-activation of these areas secondary to emotion modulation (23). Ota M et al. reported that BD patients showed a

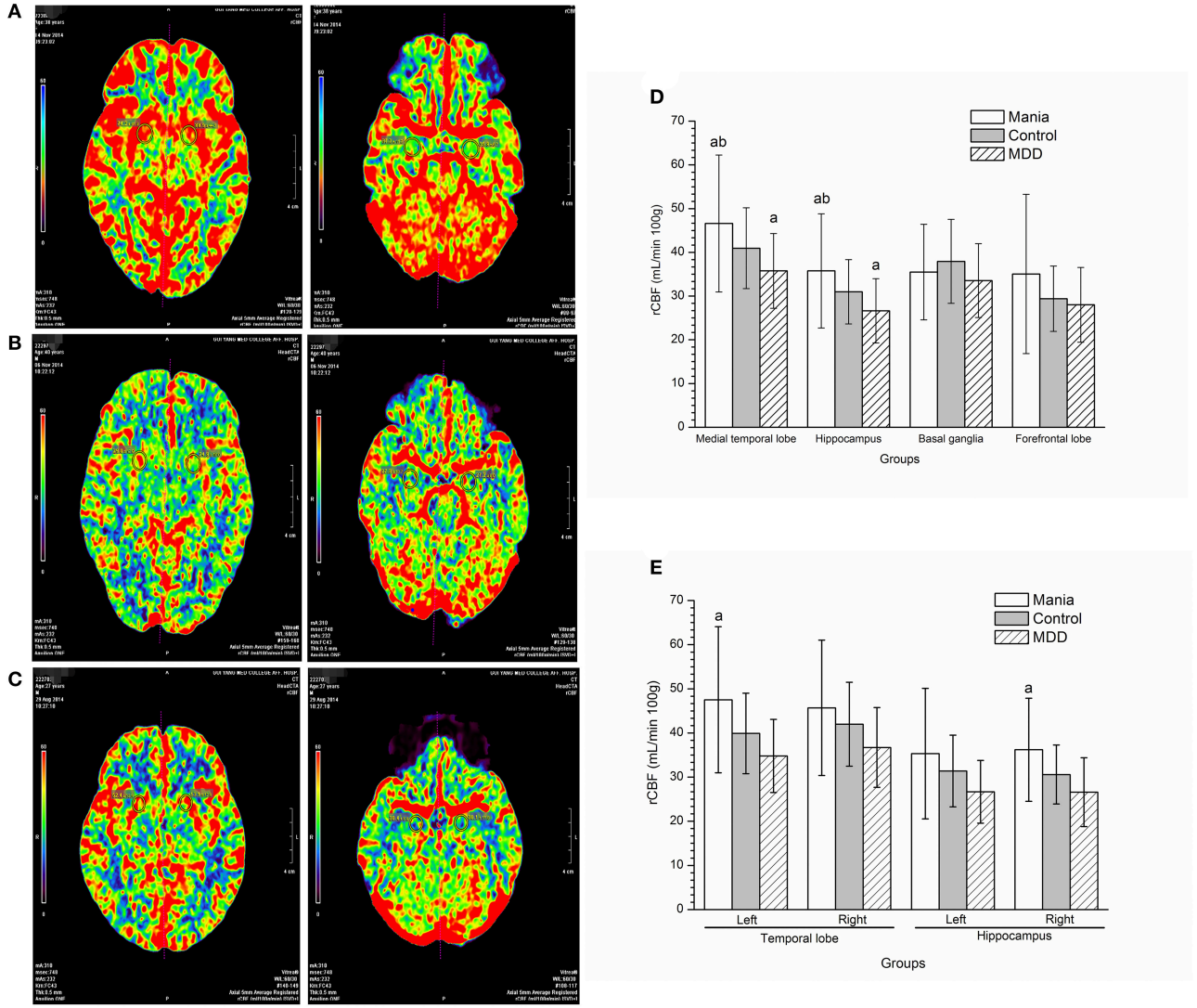

FIGURE 1 | Comparisons of regional cerebral blood flow among the mania, depression and control groups. In the picture, red represents the highest rCBF, yellow represents high rCBF, green represents low rCBF, and blue represents the lowest rCBF. **(A)** Perfusion image of the medial temporal lobe (Left) and hippocampus (Right figure) cerebral blood flow in a mania patient (male, 38 years old). **(B)** Perfusion image of the medial temporal lobe (Left) and hippocampus (Right figure) cerebral blood flow in a MDD patient (male, 40 years old). **(C)** Perfusion image of the medial temporal lobe (Left) and hippocampus (Right figure) cerebral blood flow in a normal participant (male, 37 years old). **(D)** Comparison of regional cerebral blood flow among groups. $^{a}P < 0.05$, compared with the control group, $^{b}P < 0.01$, compared with the MDD group. **(E)** Analyses of regional cerebral blood flow in left and right hemispheres among groups. $^{a}P < 0.05$, compared with the depression group.

positive correlation between rCMR (region cerebral metabolism rate) and rCBF in most regions (24). Benabarre et al. (25) found that increased rCBF in cingulate cortex was associated with decreased executive functioning in mania without treatment. In particular, O'Connel et al. found increased rCBF in striatal and temporal regions during the manic phase (26). Another study showed a reduced global CMR in the depressed state compared to controls (27), suggesting functional significance for increased temporal blood flow in mania, with an overlay of significant frontal and temporal lobe gray matter structural findings onto functional findings (28).

We specifically studied the hippocampal function, looking at its metabolism in mania. Roda et al. showed a progressive fall in hippocampal and brain gray matter density in patients with BD (29), while another study found changes in DNA methylation in the human hippocampus in bipolar disorder and schizophrenia (30). Hypothesizing as to the significance of increased blood flow in mania, we need to include this information: in the left hippocampus, there is decreased neuron integrity in mania patients (31), there are decreased hippocampal volume in BD, and we need to overlay the significance of structural findings onto functional findings (32).

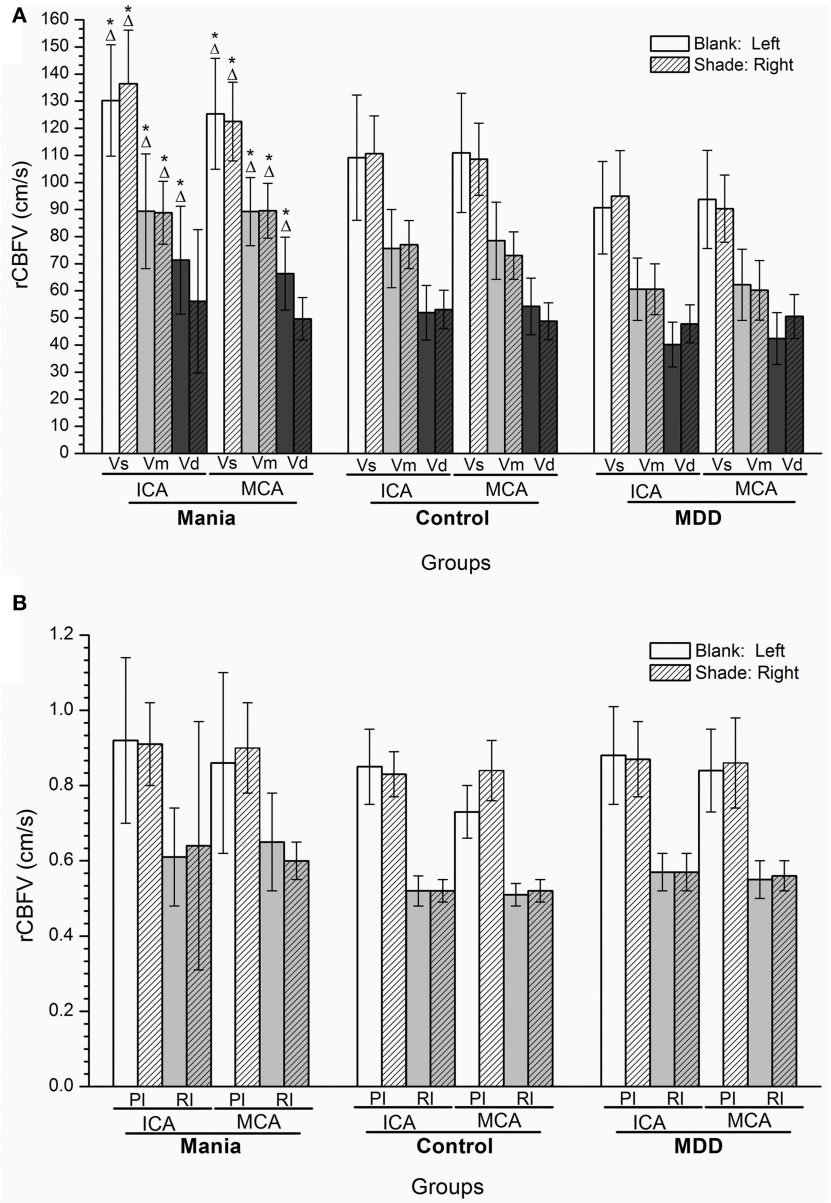

FIGURE 2 | (A,B) Histogram of regional cerebral blood flow velocity of disease groups and the control group. $^{*}P < 0.05$, Compared with the control group; $^{\Delta}P < 0.05$, Compared with the depression group. ICA, internal carotid artery; MCA, middle cerebral artery; Vs, systolic velocity; Vd, diastolic velocity; Vm, mean velocity; PI, pulsatility index; RI, resistance index.

In this study, we observed that rCBF in the left medial temporal lobe and right hippocampus was increased in the mania group, compared with the depression group. In Gonul et al.'s report (13), during BD, increased rCMR and rCBF were found in hyperactive subcortical limbic activity (including ventral striatum and amygdala) using PET or SPECT image, neuronal networks were thought to be regulated by serotonin in the limbic system, and abnormal 5-HTT density distribution in BD was relevant to the dysfunction of fronto-limbic network.

In Savitz et al.'s postmortem study in patients with bipolar disorder, reduced amygdala and hippocampus volume were observed as well (33). These structural changes positively correlate with blood oxygenated level-dependent (BOLD) activity or rCBF in response to affective or rewarding reaction after a glutamate-driven excitotoxic process.

Paralleling the above neuroimaging findings, in this study, we observed nascent evidence suggesting abnormalities in cerebral blood flow in mania. Di Tommaso examined perfusion lateralization and found right hyperperfusion and left hypoperfusion during depression, with the converse pattern in mania (34). Luo et al. observed that rCBFV increased in ACA, MCA, posterior cerebral artery, and the vertebral basilar artery

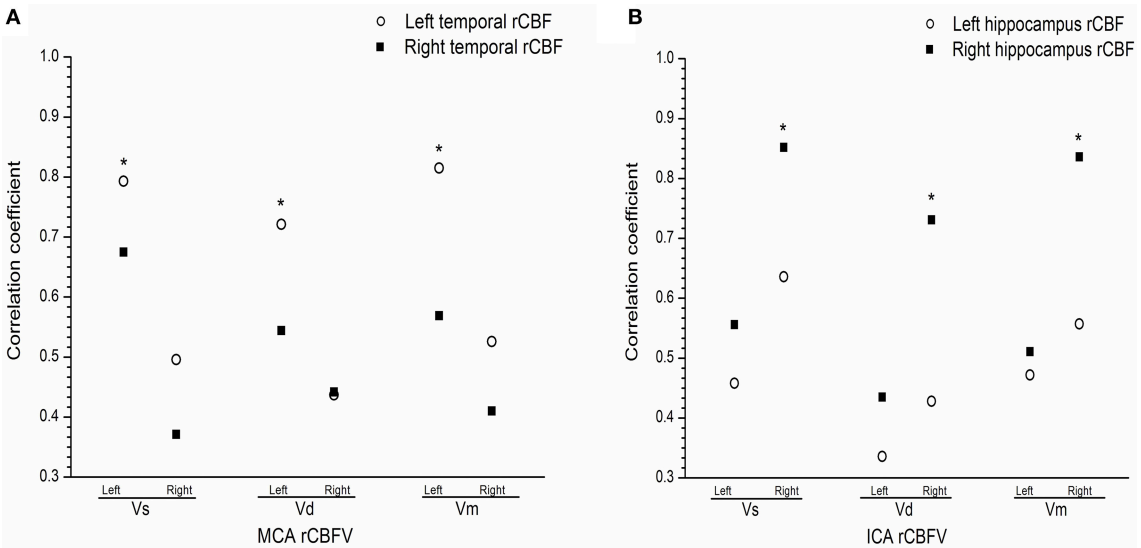

FIGURE 3 | (A) Correlation between regional cerebral blood flow and flow velocity in the medial temporal in the mania group. **(B)** Correlation between regional cerebral blood flow and flow velocity the hippocampus in the mania group. Correlation coefficient of *T*-test, $^*P < 0.05$. ICA, internal carotid artery; MCA, middle cerebral artery; L, Left; R, right; Vs, systolic velocity; Vd, diastolic velocity; Vm, mean velocity.

in patients with mania (35). Agarwal observed increased CBV in the left frontal and temporal regions in bipolar disorder (23). Although we observe that the whole blood viscosity and hematocrit are not significantly different among different groups, this phenomenon still awaits further confirmation with many more cases.

Results from limited studies using semi-quantitative measurement do not necessarily objectively reflect rCBF changes. In the study, we found that the values of Vs, Vd, and Vm of rCBFV in the left ICA and MCA were increased in mania, and the Vs and Vm values in the right ICA and MCA were similarly increased. We also observed a positive relationship between rCBFV and rCBF in the left medial temporal lobe and the right hippocampus, suggesting increased rCBFV and rCBF in the medial temporal lobe and hippocampus, largely in the left medial temporal lobe and the right hippocampus region. The increase in flow velocity is likely a compensatory mechanism to increase the regional metabolic demands. However, whole blood viscosity (including high middle low shear rate) and hematocrit are not significantly different among the three groups in our study. Of course, the changes of rCBFV and the rCBF in the brain are often affected by complex factors including physical and mental activity, sleep deprivation, temperature change, hydration level, antipsychotics, lithium, etc. In our study, some exclusion criteria were applied for all groups upon enrollment, including drugs that influence vessel compliance function, diseases of the nervous system, somatic diseases, or other significant mental disorders.

The strength of this paper is the novelty of the use of CT methodology. Given the scant literature of its use in psychiatry, more replication studies of its utility would be invaluable. While we used an active depression control group, the use of an active control group consisting of individuals with bipolar disorder in the depressive phase would have greater face validity with regards to our hypothesis. It would be useful to have other measures of cerebral bioenergetics. The sample size, while solid for an imaging study, was not extensive. Being able to contrast these CT findings with a validated measure of blood flow, however, increases the accuracy of these findings such as that these are subjects to unrecognized residual confusion due to demographic or other variables. Key more related clinical covariates need to be considered in the future study. We chose specific cerebral hemodynamic regions in patients with bipolar 1 disorder that were obtained by drawing on various regions of interests, which were perfused by the ICA, MCA, and ACA blood supplies, and

TABLE 3 | Multiple linear regression analysis for association of covariate with rCBF.

Factors	Medial temporal lobe			Hippocampus		
	St B	T	*P*-value	St B	T	*P*-value
Mania	0.206	1.785	0.032	0.197	1.546	0.021
Depression	−0.170	−1.993	0.024	−0.155	−2.034	0.018
Age	−0.321	−3.519	0.007	−0.345	−3.322	0.003

TABLE 4 | Multiple linear regression analysis for association of covariate with rCBFV.

Factors	ICA(Vs)			MCA(Vs)		
	St B	T	*P*-value	St B	T	*P*-value
Mania	0.234	1.667	0.018	0.285	2.243	0.005
Depression	−0.166	−1.006	0.015	−0.236	−2.115	0.008
Age	−0.254	−2.214	0.009	−0.245	−2.013	0.009

then by comparing them with the ROIs of the normal and depression patients. This captures representative rCBF, but not the actual value of the cerebral region flow.

We acknowledge some limitations of this study, ours was a relatively small sample taken from patients of different hospital in Guiyang city and had rCBF assessment, this could result in a possible bias, while changes in rCBF were shown, potential clinical applications need further investigate. Secondly because in recruited adults the hemodynamic specific regions in the brain were obtained by regions of interests encompassing the regions of white and gray matter, and then comparing them with the regions of the normal brain, this captured representative rCBF, there may be little difference compared with the real value of the regions of the brain.

CONCLUSIONS

Our results suggest that rCBF is increased in the medial temporal lobe and hippocampus in mania patients. There are prominent changes in the left medial temporal lobe and the right hippocampus region, accompanied by increased rCBFV in the left MCA and the right internal carotid artery (ICA). It will be interesting to study how the changes observed in this study respond to clinical therapy. We believe that the patients with mania were found out the regional cerebral perfusion pattern, realize more patients accompanying emotional high, thinking active, energetic, along with the land transfer and cognitive dysfunction may be linked to increased blood flow to the brain, cerebral blood flow velocity, the rapid proposed theory support for clinical application. Therefore monitoring rCBF in cerebral hemispheres of mania is in order to clarify its potential utility to psychiatric disorder for possible diagnostic and treatment response purposes; furthermore, the treatment of patients with mania in clinical work may pay more attention to the changes of patients' cerebral blood supply.

AUTHOR CONTRIBUTIONS

YW and XL wrote the paper. PL, HZ, QL, LY, LZ, and PX performed research. LL and DL designed experiments. DF analyzed data.

FUNDING

This study was supported by two Grant from the National Natural Science Foundation of China, Project Grant: [2017] NO 81761128036, [2017] NO 31760294, [2015] NO 81560235, as well as supports from High-level Innovative Talents Cultivation Program of Guizhou Province (Qian Ke He SY [2016]5679, [2018]5802).

ACKNOWLEDGMENTS

We would like to thank Drs. Fred Bogott at the Austin Medical Center, Austin of Minnesota for his excellent English editing of the manuscript.

REFERENCES

1. Scott J, Murray G, Henry C, Morken G, Scott E, Angst J, et al. Activation in bipolar disorders: a systematic review. *JAMA Psychiatry* (2017) 74:189–96. doi: 10.1001/jamapsychiatry.2016.3459
2. Morris G, Walder K, McGee SL, Dean OM, Tye SJ, Maes M, et al. A model of the mitochondrial basis of bipolar disorder. *Neurosci Biobehav Rev*. (2017) 74:1–20. doi: 10.1016/j.neubiorev.2017.01.014
3. Caliyurt O, Altiay G. Resting energy expenditure in manic episode. *Bipolar Disord*. (2009) 11:102–6. doi: 10.1111/j.1399-5618.2008.00649.x
4. Takeda T, Konno M, Kawakami Y, Suzuki Y, Kawano Y, Nakajima K, et al. Influence of pleasant and unpleasant auditory stimuli on cerebral blood flow and physiological changes in normal subjects. *Adv Exp Med Biol*. (2016) 876:303–9. doi: 10.1007/978-1-4939-3023-4_38
5. Chen CH, Suckling J, Lennox BR, Ooi C, Bullmore ET. A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disord*. (2011) 13:1–15. doi: 10.1111/j.1399-5618.2011.00893.x
6. Blumberg HP, Stern E, Martinez D, Ricketts S, de Asis J, White T, et al. Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry* (2000) 48:1045–52. doi: 10.1016/S0006-3223(00)00962-8
7. Chang K, Garrett A, Kelley R, Howe M, Sanders EM, Acquaye T, et al. Anomalous prefrontal-limbic activation and connectivity in youth at high-risk for bipolar disorder. *J Affect Disord*. (2017) 222:7–13. doi: 10.1016/j.jad.2017.05.051
8. Yuksel C, Du F, Ravichandran C, Goldbach JR, Thida T, Lin P, et al. Abnormal high-energy phosphate molecule metabolism during regional brain activation in patients with bipolar disorder. *Mol Psychiatry* (2015) 20:1079–84. doi: 10.1038/mp.2015.13
9. Johnson CP, Follmer RL, Oguz I, Warren LA, Christensen GE, Fiedorowicz JG, et al. Brain abnormalities in bipolar disorder detected by quantitative T1rho mapping. *Mol Psychiatry* (2015) 20:201–6. doi: 10.1038/mp.2014.157
10. Bhardwaj R, Chakrabarti S, Mittal BR, Sharan P. A single photon emission computerized tomography (SPECT) study of regional cerebral blood flow in bipolar disorder. *World J Biol Psychiatry* (2010) 11:334–43. doi: 10.3109/15622970802575977
11. Amen DG, Krishnamani P, Meysami S, Newberg A, Raji CA. Classification of depression cognitive disorders and co-morbid depression and cognitive disorders with perfusion SPECT neuroimaging. *J Alzheimers Dis*. (2017) 57:253–66. doi: 10.3233/JAD-161232
12. Wolf ME. Functional TCD: regulation of cerebral hemodynamics–cerebral autoregulation vasomotor reactivity and neurovascular coupling. *Front Neurol Neurosci*. (2015) 36:40–56. doi: 10.1159/000366236
13. Gonul AS, Coburn K, Kula M. Cerebral blood flow metabolic receptor and transporter changes in bipolar disorder: the role of PET and SPECT studies. *Int Rev Psychiatry* (2009) 21:323–35. doi: 10.1080/09540260902962131
14. Lanzman B, Heit JJ. Advanced MRI measures of cerebral perfusion and their clinical applications. *Top Magn Reson Imaging* (2017) 26:83–90. doi: 10.1097/RMR.0000000000000120
15. Siebert E, Bohner G, Masuhr F, Deuschle K, Diekmann S, Wiener E, et al. Neuroimaging by 320-row CT: is there a diagnostic benefit or is it just another scanner? A retrospective evaluation of 60 consecutive acute neurological patients. *Neurol Sci*. (2010) 31:585–93. doi: 10.1007/s10072-010-0292-7
16. Zhang B, Gu GJ, Jiang H, Guo Y, Shen X, Li B, et al. The value of whole-brain CT perfusion imaging and CT angiography using a 320-slice CT scanner in the diagnosis of MCI and AD patients. *Eur Radiol*. (2017) 27:4756–66. doi: 10.1007/s00330-017-4865-1
17. Wang Y, Zhang H, Tang S, Liu X, O'Neil A, Turner A, et al. Assessing regional cerebral blood flow in depression using 320-slice computed tomography. *PLoS ONE* (2014) 9:e107735. doi: 10.1371/journal.pone.0107735
18. World Medical Association. Human experimentation: code of ethics of the World Medical Association (Declaration of Helsinki). *Can Med Assoc J*. (1964) 91:619.

19. Hua Y, Gao S, Wu G, Pan X, Qian S. A guide for operation norm and diagnostic criteria of transcranial doppler. *Chin J Med Ultrasound*. (2008) 5:2–6.
20. Siebert E, Bohner G, Dewey M, Masuhr F, Hoffmann KT, Mews J, et al. 320-slice CT neuroimaging: initial clinical experience and image quality evaluation. *Br J Radiol*. (2009) 82:561–70. doi: 10.1259/bjr/27721218
21. Benson BE, Willis MW, Ketter TA, Speer A, Kimbrell TA, Herscovitch P, et al. Differential abnormalities of functional connectivity of the amygdala and hippocampus in unipolar and bipolar affective disorders. *J Affect Disord*. (2014) 168:243–53. doi: 10.1016/j.jad.2014.05.045
22. Deckersbach T, Dougherty DD, Savage C, McMurrich S, Fischman AJ, Nierenberg A, et al. Impaired recruitment of the dorsolateral prefrontal cortex and hippocampus during encoding in bipolar disorder. *Biol Psychiatry* (2006) 59:138–46. doi: 10.1016/j.biopsych.2005.06.030
23. Agarwal N, Bellani M, Perlini C, Rambaldelli G, Atzori M, Cerini R, et al. Increased fronto-temporal perfusion in bipolar disorder. *J Affect Disord*. (2008) 110:106–14. doi: 10.1016/j.jad.2008.01.013
24. Ota M, Sato N, Sakai K, Okazaki M, Maikusa N, Hattori K, et al. Altered coupling of regional cerebral blood flow and brain temperature in schizophrenia compared with bipolar disorder and healthy subjects. *J Cereb Blood Flow Metab*. (2014) 34:1868–72. doi: 10.1038/jcbfm.2014.151
25. Benabarre A, Vieta E, Martinez-Aran A, Garcia-Garcia M, Martin F, Lomena F, et al. Neuropsychological disturbances and cerebral blood flow in bipolar disorder. *Aust N Z J Psychiatry* (2005) 39:227–34. doi: 10.1080/j.1440-1614.2004.01558.x
26. O'Connell RA, Van Heertum RL, Luck D, Yudd AP, Cueva JE, Billick SB, et al. Single-photon emission computed tomography of the brain in acute mania and schizophrenia. *J Neuroimaging* (1995) 5:101–4. doi: 10.1111/jon199552101
27. Mitelman SA, Bralet MC, Mehmet Haznedar M, Hollander E, Shihabuddin L, Hazlett EA, et al. Positron emission tomography assessment of cerebral glucose metabolic rates in autism spectrum disorder and schizophrenia. *Brain Imaging Behav*. (2017) 12:532–46. doi: 10.1007/s11682-017-9785-9
28. Anderson D, Ardekani BA, Burdick KE, Robinson DG, John M, Malhotra AK, et al. Overlapping and distinct gray and white matter abnormalities in schizophrenia and bipolar I disorder. *Bipolar Disord*. (2013) 15:680–93. doi: 10.1111/bdi.12096
29. Roda A, Chendo I, Kunz M. Biomarkers and staging of bipolar disorder: a systematic review. *Trends Psychiatry Psychother*. (2015) 37:3–11. doi: 10.1590/2237-6089-2014-0002
30. Ruzicka WB, Subburaju S, Benes FM. Circuit- and diagnosis-specific DNA methylation changes at gamma-aminobutyric acid-related genes in postmortem human hippocampus in schizophrenia and bipolar disorder. *JAMA Psychiatry* (2015) 72: 541–51.
31. Haarman BC, Burger H, Doorduin J, Renken RJ, Sibeijn-Kuiper AJ, Marsman JB, et al. Volume metabolites and neuroinflammation of the hippocampus in bipolar disorder–a combined magnetic resonance imaging and positron emission tomography study. *Brain Behav Immun*. (2016) 56:21–33. doi: 10.1001/jamapsychiatry.2015.49
32. Otten M, Meeter M. Hippocampal structure and function in individuals with bipolar disorder: a systematic review. *J Affect Disord*. (2015) 174:113–25. doi: 10.1016/j.jad.2014.11.001
33. Savitz J, Drevets WC. Neuroimaging and neuropathological findings in bipolar disorder. *Curr Top Behav Neurosci*. (2011) 5:201–25. doi: 10.1007/7854_2010_68
34. Di Tommaso MC. A comparative study of bipolar disorder and attention deficit hyperactivity disorder through the measurement of regional cerebral blood flow. *J Biol Regul Homeost Agents* (2012) 26:1–6.
35. Luo L. Detection and study of cerebral blood flow using TCD in patients with schizophrenia and mania. *Chin Jiangxi Med*. (2008) 43:354–6.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 28 August 2018
doi: 10.3389/fpsyt.2018.00382

A Systematic Review of Cognitive Predictors of Treatment Outcome in Major Depression

Samantha J. Groves[1], *Katie M. Douglas*[1] *and Richard J. Porter*[1,2]*

[1] *Department of Psychological Medicine, University of Otago, Christchurch, New Zealand,* [2] *Specialist Mental Health Services, Canterbury District Health Board, Christchurch, New Zealand*

Background: Research suggests that only 50% of patients with major depression respond to psychotherapy or pharmacological treatment, and relapse is common. Therefore, there is interest in elucidating factors that help predict clinical response. Cognitive impairment is a key feature of depression, which often persists beyond remission; thus, the aim of this systematic review was to determine whether baseline cognitive functioning can predict treatment outcomes in individuals with depression.

Method: Studies examining cognitive predictors of treatment response in depression were identified using Pub Med and Web of Science databases. Given the heterogeneity of outcome measures, the variety of treatment protocols, and the differing ways in which data was presented and analyzed, a narrative rather than meta-analytic review technique was used.

Results: 39 studies met inclusion criteria. Findings in younger adult samples were inconclusive. There was some evidence for a predictive effect of executive function and to a lesser extent, psychomotor speed, on treatment response. There was no evidence of learning or memory being associated with treatment response. In older-aged samples, the evidence was much more consistent, suggesting that poor executive function predicts poor response to SSRIs.

Conclusions: Findings from the present review suggest that certain aspects of cognitive functioning, particularly executive function, may be useful in predicting treatment response in depression. This is certainly the case in elderly samples, with evidence suggesting that poor executive functioning predicts poor response to SSRIs. With further research, baseline cognitive functioning may serve as a factor which helps guide clinical decision making. Moreover, cognitive deficits may become targets for specific pharmacological or psychological treatments, with the hope of improving overall outcome.

Keywords: major depression, cognitive predictors, cognitive function, treatment response, relapse, remission, executive function

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Rebecca Strawbridge,
King's College London,
United Kingdom
Andre F. Carvalho,
Centre for Addiction and Mental Health, Canada

***Correspondence:**
Richard J. Porter
richard.porter@otago.ac.nz

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *03 May 2018*
Accepted: *30 July 2018*
Published: *28 August 2018*

Citation:
Groves SJ, Douglas KM and Porter RJ (2018) A Systematic Review of Cognitive Predictors of Treatment Outcome in Major Depression. Front. Psychiatry 9:382. doi: 10.3389/fpsyt.2018.00382

INTRODUCTION

Major depression is among the leading causes of global disability (1) and although our understanding of the disorder is growing, treatment outcomes remain unsatisfactory. Research indicates that only 50% of patients respond to psychotherapy or pharmacological treatment and relapse is common (2, 3). Clinical factors predict differential response to treatments to a limited extent, leaving clinicians to choose first-line treatment on the basis of likely side effects, availability and their own clinical experience (4). With each treatment failure, there is an increased risk of both longer-term failure to respond to treatment and of relapse (5). In this context, there has been increased interest in elucidating factors that help predict clinical response in depression, including cognitive factors, hormonal measures, and neural markers.

Cognitive functioning is relatively easy to measure in clinical practice, and if found to be predictive of treatment response, it has the potential to be widely used. Evidence indicates that depression is associated with widespread cognitive deficit, including impairments in executive functioning, attention, verbal learning and memory, visual learning and memory, emotional processing and psychomotor speed (6). Although aspects of these cognitive deficits may resolve following successful treatment for some individuals, it is often the case that they persist beyond remission (7, 8).

If baseline cognitive deficits are predictive of eventual response, then such deficits could be targeted by specific pharmacological or psychological treatments, in the hope of improving overall outcome. For example, the antidepressant Vortioxetine has been shown to improve psychomotor and verbal memory function in moderate to severe depression (9), while RU486 has been shown to improve spatial working memory in the depressed phase of bipolar disorder (10). Considerable research is currently occurring into psychological techniques that aim to improve cognitive function in depression (11). Indeed, studies that have specifically targeted executive dysfunction in elderly depressed patients, have found positive effects (12). However, due to the intensive nature of such psychological treatments, it is likely that these techniques need to be aimed at those who would have otherwise experienced a more difficult and prolonged recovery. A further implication of finding cognitive predictors of treatment response is that if cognitive impairment is known to predict poorer outcomes, then this may prompt a more aggressive approach in the initial stages of treatment. For example, a clinician may use a combination of psychotherapy and pharmacotherapy in situations where only one of these modalities would have been typically used.

The aims of the present review were therefore as follows: (i) to examine findings from studies investigating cognitive predictors of treatment response in depression, and (ii) to examine the methodological issues arising from the studies that have examined this. We reviewed all the available literature in which cognitive testing was conducted at baseline, to determine whether aspects of cognitive functioning would impact on treatment outcomes.

Research Questions

1. Does baseline cognitive functioning predict treatment outcomes in major depression?
2. Is the predictive relationship dependent on treatment modality?

METHODS

Protocol and Registration

Details of the protocol for this systematic review were registered on PROSPERO (42018081980) and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42018081980.

Search Strategy

Up to 1 December 2017, a systematic review of electronic databases was carried out for relevant papers using Pub Med and Web of Science. In the initial search, the following search items were used "major depression" or "depression" and "neuropsychological predictors" or "cognitive predictors" and "treatment response." To ensure inclusion of all available articles, reference lists of all relevant papers were checked. Further, Web of Science was used to review articles that had cited the relevant articles found using the aforementioned search strategies, enabling the inclusion of more recent publications.

Inclusion Criteria

Any peer-reviewed article involving baseline assessment of cognitive functioning, a proposed active treatment of depression and a follow up measure of depression severity, were included in the present review. All subtypes of depression were also included (unipolar or bipolar - depressed phase, psychotic or non-psychotic). "Treatment" could be pharmacotherapy, electroconvulsive therapy (ECT), transcranial stimulation (direct current or magnetic), psychotherapy, or cognitive remediation (CR). Studies were required to use adult samples, with all participants 18 years of age or older.

Exclusion Criteria

Reasons for exclusion were: (i) use of a depressed sample with comorbid major medical, neurological or endocrinological conditions, (ii) inclusion of individuals scoring <24 on a Mini Mental Status Exam ($n = 6$), and (iii) not presenting data on baseline depression severity ($n = 1$). All studies were limited to English-language publications.

Full Study Review

Articles were initially screened by two of the reviewers who independently reviewed the titles and abstracts of studies, to accept or reject for full text review. The same two reviewers then examined the full texts of the studies that had passed initial screening, to determine if they still met inclusion criteria. If inclusion of a paper was unclear, then all three co-authors discussed in order to achieve a consensus. Data was extracted from eligible studies into a spreadsheet. For each study, we extracted the following data: (1) characteristics of the sample, including sample size, average age and baseline

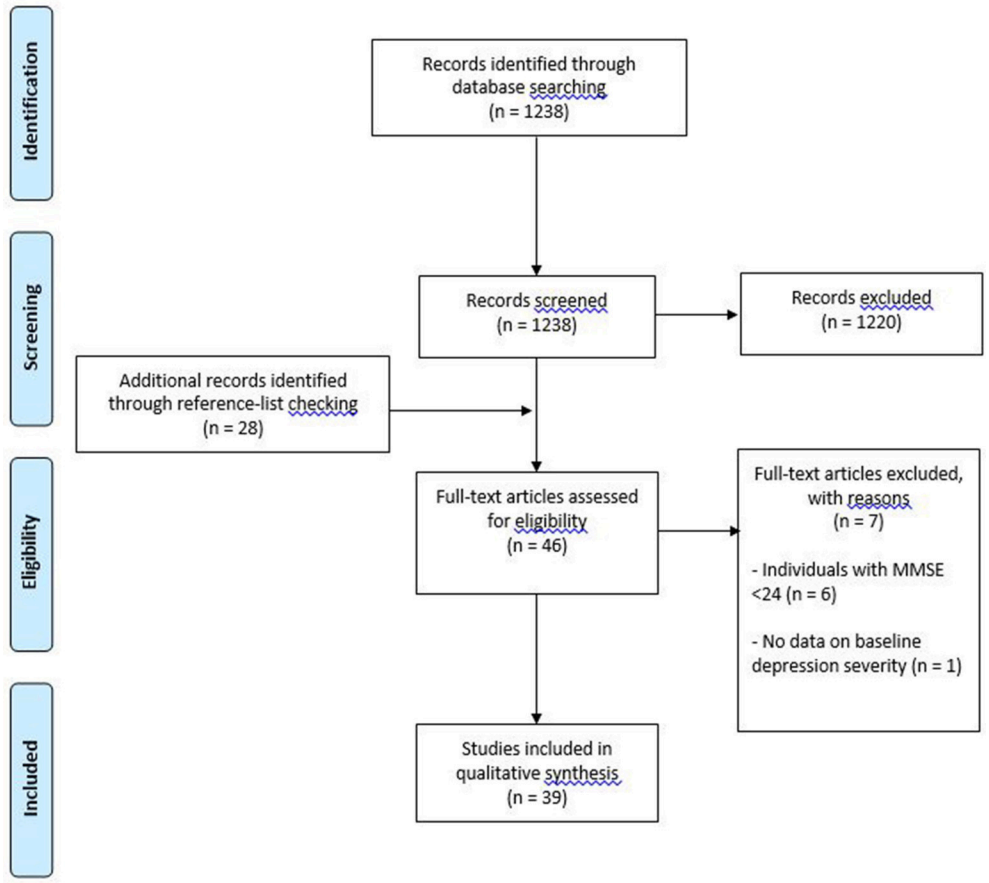

FIGURE 1 | PRISMA flow diagram of studies retrieved for the review.

depression severity, (2) study design, (3) cognitive tests used during assessment, (4) response/remission criteria, and (5) study outcomes.

RESULTS

Study Characteristics

Thirty-nine studies met inclusion criteria (see **Figure 1** for flow diagram of studies retrieved for review). Of these studies, 32 used pharmacotherapy as the primary treatment (18 single antidepressant, 14 mixed antidepressant treatment); 1 study used pharmacotherapy, psychotherapy and a combination thereof; 1 study used unrestricted pharmacotherapy treatment in addition to ECT (the latter being the final treatment option); 1 study used transcranial direct current stimulation; 1 study used deep brain stimulation, and 3 studies used psychosocial interventions (see **Tables 1**, **2**). Regarding the term "mixed antidepressant treatment," we refer to a number of possible situations. Firstly, open label treatment with a specific type of antidepressant but with the option to use various antidepressants within that class; secondly, open label treatment with any type of antidepressant; and thirdly, a standardized treatment algorithm allowing for treatment changes according to response. In one of the pharmacological studies (47), a small proportion of the sample received ECT in conjunction with pharmacotherapy (4 out of 100 participants). Given the small number of participants receiving adjunctive ECT, it was decided to group this study with others involving mixed antidepressant treatment. An additional pharmacological study (55) utilized ECT as a final treatment option. Given that 48% of the participants were treated with ECT, it was decided to group this study with the "other biological" treatment studies. One study utilized a naturalistic treatment protocol (38), which meant that some of the participants received no recognized treatment ($n = 4$). Because most participants received some form of antidepressant medication, it was decided to include the study in this review.

Studies used a range of cognitive tests and the clinical characteristics of the depressed samples varied substantially across studies. In this review, more emphasis is placed on those studies with the greatest number of participants, as they have more statistical power. While we did not formally rate the quality of studies, we have discussed methodological strengths and weaknesses and taken this into account in synthesizing the evidence. In the sections that follow, the studies will be briefly discussed according to treatment type, and findings will be further divided into different cognitive domains. It is important

TABLE 1 | Reviewed studies using antidepressant treatment during the follow-up period.

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
ANTIDEPRESSANT MONOTHERAPY							
(13)	14 MDE	41.86 (13.77)	HDRS: 22.86	9-week randomized, double-blind placebo controlled trial of Fluoxetine.	WAIS-R Digit Span, Digit Symbol & Block Design; TMT-A & B; Stroop parts A, B & C, Boston Naming Test, Rey Complex Figure Test, Benton Faces, RAVLT, WMS-R Visual Reproduction; WCST; Auditory Consonant Trigrams; COWAT.	Responder = HDRS <10 and no longer met criteria for MDE	8 responders, 6 non-responders to active treatment. Non-responders significantly worse performance on WCST and more errors on Stroop Test.
(14)	37 MDD	Responders – 37.92 (10.77) Non-responders- 33.08 (9.38)	HDRS17: Responders-16.16 (3.57) Non-responders- 17.33 (5.74)	12-week open trial of Fluoxetine	COWAT; SCWT; WCST; WAIS-III Digit Symbol, Block Design, Digit Span &Vocabulary.	Responders-no longer met criteria for MDD and had CGI scale score of much improved or very much improved.	25 responders, 12 non-responders. Non-responders had fewer words on COWAT and named fewer colors on Stroop (ES of 1.44 and 0.74 respectively). COWAT scores significantly predicted outcome of HDRS scores.
(15)	26 MDD outpatients	24.46 (4.72)	HDRS-17: 24.75 (5.61)	8-week trial of Bupropion-SR (150 mg/d)	WAIS III Digit Span, Delayed Match to Sample, Spatial Span, RAVLT, Pattern Recognition Memory, Paired Associates Learning, Spatial Recognition Memory, Match to Sample Visual Search, Reaction Time, RVIP, Stroop, COWAT, Intra-Extra Dimensional Set Shift, Spatial Working Memory, Stockings of Cambridge.	Response ≥ 50% decrease in HDRS-17 at end of 8 weeks.	12 responders, 8 non-responders. Responders performed more poorly on Paired Associates Learning and Stockings of Cambridge at baseline (small ES).
(16–18)	72 MDD	31.18 (7.56)	HDRS-17: 21.47 (2.81)	12-week Fluoxetine treatment (20 mg/d)	WAIS III Digit Span, Spatial Working Memory, RAVLT, Paired Associates Learning, Delayed Matching to Sample, Stroop, RVIP, COWAT, Intra-Extra Dimensional Set Shift, Stockings of Cambridge.	Response ≥ 50% decrease in HDRS-17 at end of 4 weeks. Remission = HDRS-17 of 6 or lower at 12 weeks.	2010: After 4 weeks, 42 responders, 22 non-responders, 8 dropouts. Responders performed better on Digit Span forwards and were faster with their initial thinking time on Stockings of Cambridge compared with non-responders. In contrast, responders had slower mean subsequent thinking time on Stockings of Cambridge. 2012: Analyses included data from 56 participants. Forty-three participants remitted by 12 weeks; however, no cognitive variables predicted remission. 2013: Analyses included all 72 participants. Of the 51 remitters, those with slower processing speed (Stroop) and poorer Spatial Working Memory performance were slower to remit.

(Continued)

TABLE 1 | Continued

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
(19)	13 MDD (treatment resistant)	52	HDRS-17: 20.3 (4.3)	Six infusions of Ketamine Hydrochloride (0.5 mg/kg over 40 min) over 12-day period	CogState Battery	Response = ≥ 50% reduction in MADRS score. Remission = ≤ 9 MADRS.	The likelihood of responding to six Ketamine infusions was greater amongst those with poor attention at baseline.
(20)	1008 MDD (655 completers) 336 HC	MDD: Intact - 35 (11.6) Impaired-45.6 (11.9) HC - 37.0 (13.1)	HDRS-17: Intact- 21.7 (3.9) Impaired- 22.4 (4.5)	8-week trial of either Escitalopram, Sertraline or Venlafaxine-ER.	Motor Tapping; Choice Reaction Time; Memory Recall; Digit Span; SCWT; Continuous Performance Test; Go/No-Go, Switching of Attention; Executive Maze; Explicit Emotion Identification & Emotion Attention Bias.	Remission = HDRS-17 ≤ 7 or QIDS ≤ 5. Response ≥ 50% decrease on HDRS or QIDS	Cluster analysis showed MDD participants fell into 2 sub-groups: intact (735) and impaired (273); the latter, performed below the healthy norm for 11/13 aspects of functioning. Impairments greatest in patients predicted to be non-remitters to Escitalopram for attention, decision speed, working memory and speed of emotion identification.
(21)	25 MDD	43.7 (12.5)	HDRS-17 = 22.2 (4.9)	6-week Duloxetine treatment (65.8 mg ± 16.1)	Test Battery for Attentional Performance.	Response = ≥ 50% reduction in HDRS score	Greater alertness and divided attention were associated with lower HDRS scores, post-treatment.
(22)	25 MDD (treatment resistant)	Responders: 53.81 Non-responders: 40.44	MADRS: Responders = 36.88 Non-responders = 37	Open label, single infusion of Ketamine Hydrochloride (0.5 mg/kg over 40 min)	Tests from MCCB: TMT-A, WMS III Spatial Span, BACS Digit Symbol, Letter-Number Sequencing, Hopkins Verbal Learning Test, Brief Visual Memory Test, Category Fluency, Continuous Performance Test.	Response = ≥ 50% reduction in MADRS score, 24 h following baseline assessment.	Psychomotor speed predicted response to Ketamine. Responders were significantly more impaired than non-responders in the domains of psychomotor speed, working memory and composite MCCB.
(23)	43 MDD (treatment resistant)	47.1 (12.6)	MADRS = 32.5 (6.0)	Double-blind, single infusion of either Ketamine Hydrochloride (0.5 mg/kg) or Midazolam (0.045 mg/kg) over 40 min; latter served as active placebo.	Tests from MCCB: TMT-A, WMS III Spatial Span, BACS Digit Symbol, Letter-Number Sequencing, Hopkins Verbal Learning Test, Brief Visual Memory Test, Neuropsychological Assessment Battery Mazes, Category Fluency.	Response = ≥ 50% reduction in MADRS score. Primary outcome was change in MADRS score 24 h following treatment. Secondary outcomes included MADRS score at 48 and 72 h and 7 days following treatment.	Psychomotor speed predicted response to Ketamine, whereby slow psychomotor speed at baseline was associated with improved antidepressant response to Ketamine. Responders were significantly more impaired than non-responders in the domain of psychomotor speed.
(24)	508 MDD	Remitters −47 (12.7) Non-remitters−45.2 (11.9)	QIDS-SR: Remitted-15.5 (5.2) NR-16.1 (4.4)	Multicentre study conducted in naturalistic setting in 388 community psychiatric centers. 6–8 weeks of Agomelatine (25–50 mg)	D2 Cancellation Test; TMT-A & B.	QIDS-SR ≤ 5 at 6–8 weeks	The number of omission mistakes on D2 (attention) predicted clinical and functional remission (with a dose-effect). Fewer mistakes associated with better outcomes.

(Continued)

TABLE 1 | Continued

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
(25)	272 MDD	Long term psychodynamic psychotherapy-−29.9 (2.43) Fluoxetine-29.64 (2.21) Combination-29.39 (1.01)	BDI: Long term psychodynamic psychotherapy −27.36 (3.82) Fluoxetine-29.64 (2.71) Combination-29.39 (3.85)	24 months of long-term psychodynamic psychotherapy ($n = 90$), Fluoxetine treatment ($n = 91$) or a combination thereof ($n = 90$)	WAIS III: Vocabulary, Similarities, Arithmetic, Digit Span, Information, Comprehension, Letter-number Sequencing, Picture Completion, Digit-symbol Coding, Block Design, Matrix Reasoning, Picture Arrangement, Symbol Search, Object Assembly.	Conducted mixed model analyses-no remission/response criteria	Higher Letter-number Sequencing and Matrix Reasoning scores at baseline, predicted lower BDI scores at 24 months. Higher Similarities scores at baseline predicted higher BDI scores at 24 months. Higher baseline Digit-Symbol Coding scores predicted lower BDI scores in patients who received Fluoxetine, and higher BDI scores in patients receiving psychodynamic therapy or combined treatment, at 24 months.
(26)	22 MDE	Remitted-70.2 (7.4). Non-remitters-74.9 (8.1)	HDRS: Remitters-21.7. Unremitters-25.4	6-week trial of Citalopram	MDRS-five domains: attention, Initiation/Perseveration, construction, conceptualisation and memory.	Remission ≤ 10 HDRS	13 patients remitted and 9 remained symptomatic. I/P scores were lower in those who did not remit vs. those who did.
(27)	444 MDD (217 Sertraline, 119 Fluoxetine, 104 Nortriptyline)	Sertraline group - 68.0 (5.7) Fluoxetine group - 67.4 (5.9) Nortriptyline group - 67.9 (6.6)	HDRS-24: Sertraline group-24.9 (4.6) Fluoxetine group-25.0 (4.7) Nortriptyline group-24.8 (5.2)	Two double-blind 12-week studies comparing Sertraline (50 mg per day), to Fluoxetine (20 mg per day) and to Nortriptyline (25 mg per day).	Buschke-Fuld Selective Reminding Test, Digit Symbol Substitution Task & MMSE.	Responder status defined as a CGI-I score of "much" or "very much" improved.	Cognitive scores did not significantly predict endpoint improvement in depression, nor time to respond.
(28, 29)	112 MDD	Remitters-71.56 (6.4) Non-remitters-75.1 (6.15)	HDRS: Remitters-23.13 Non-remitters-25.76	8-week trial of Citalopram	Initiation/Perseveration subscale of the MDRS and SCWT	Remission ≤ 10 HDRS Responders ≥ 50% change on HDRS.	2004: 61 remitters and 51 non-remitters. Lower I/P scores were associated with longer time to remission and poor remission rate. Lower Stroop scores were associated with poor remission rate. 2005: I/P scores below the median (≤ 35) and Stroop scores at the lowest quartile (≤ 22) predicted less change in depressive symptoms. Thus, poorer executive function performance was associated with poor treatment response.
(30)	12 MDD	Remitters −71.2 (5.0) Non-remitters-68.8 (6.3)	HDRS: Remitters-19.2 (2.6) Non-remitters-22.0 (6.7)	8-week open-controlled trial of Escitalopram (10 mg/day).	MMSE, MDRS, Hopkins Verbal Learning Test, WCST, Emotional Go/No-Go	Student's *t*-test between remitters and non-remitters	No significant differences between remitters and non-remitters in overall cognitive impairment, memory, performance on the WCST, and error rates or reaction time on the Emotional Go/No-Go Task.
(31)	13 MDD 13 HC	71.5 (6.7)	HDRS-24: 18.	8-week trial of Citalopram	Attention Network Test	Time to remission: 1st day of a 2-week period where a patient didn't meet diagnostic criteria and HDRS <10.	Significant correlation between conflict scores (measure of executive function) and time to remission. Those with greater cost reaction time due to incongruent flankers took longer to remit.

(Continued)

TABLE 1 | Continued

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
(32, 33)	84 MDD	79	HDRS-24: 24	8-week multisite, randomized, placebo controlled trial of Citalopram (20–40 mg/d)	2007: SCWT measured response inhibition (defines as the highest quartile of the distribution). 2008: MMSE, WASI-III Digit Symbol Substitution, Choice Reaction Time, Judgement of Line Orientation, Buschke Selective Reminding Test.	2007: Using growth curves to examine the association between baseline response inhibition and depression severity at 8 weeks. 2008: Remission = HDRS <10 Response = 50% reduction in HDRS over 8-week treatment period.	2007: Individuals classified as having high response inhibition had higher HDRS scores (poorer response) at 8 weeks, than those who did not. 2008: No association between treatment response and cognitive impairment. Impairment on Digit Symbol test was associated with slower treatment response.
(34)	70 MDD	Remitters: 70.1 (5.8) Non-remitters: 70.4 (7.1)	HDRS-24: Remitters = 21.8 (4.1) Non-remitters = 22.4 (3.7)	12-week Escitalopram trial (10 mg/d).	MDRS Initiation/Perseveration subscale, Simple Verbal Initiation/Perseveration, TMT-A, Hopkins Verbal Learning Test-Revised, WCST.	Remission = HDRS-24 ≤ 7 for 2 consecutive weeks and no longer met DSM-IV criteria for depression.	Worse performance on MDRS I/P (particularly complex verbal subscale) associated with poorer remission rates.
(35)	53 MDD 30 HC	MDD-72.18 (7.56) HC-72.83 (5.95)	HDRS: 23.4 (3.9)	12-week Escitalopram (target daily dose 20 mg).	SCWT, Tower of London, MDRS-Initiation/Perseveration and Iowa Gambling Test.	Remission-HDRS ≤ 10.	Individuals who were impaired on the Stroop, Tower of London and MDRS- I/P had a smaller reduction in depressive symptoms than those who were only impaired on the Iowa Gambling Task or those who were unimpaired. Further, this group demonstrated a lower probability of achieving remission than the other groups.
MIXED ANTIDEPRESSANT TREATMENT							
(36)	16 single MDE 32 recurrent MDE 4 BD	Responders−48.73 (11.04) Non-responders-49.28 (10.14)	HDRS-17: Responders-48.73 (11.04) Non-responders-49.28 (10.14)	First phase, Maprotiline or Nortryptiline and co-medication with Lunitrazepam, Lormetazepam or placebo. Second phase, non-responders switched from trycyclics, to either Brofaromine or Tranylcypromine. Both phase were 4 weeks each.	COWAT; Sentence Repetition; Ten Words Test; Perceptual Speed; Facial Recognition Test; Judgement of Line Orientation	Response ≥ 50% improvement on HDRS at end-treatment. Multivariate analysis conducted between responders and non-responders.	No significant differences between responders and non-responders in baseline cognitive performance.
(37)	36 single MDE 32 recurrent MDE 5 BD	45.6	HDRS-21: 29.2 MADRS: 33.52	4 weeks of antidepressant treatment, followed up 6 months later to assess relapse.	Test Battery for Attentional Performance; Zahlenverbindungstest; D2 Cancellation Task; Selective Attention Test; SCWT; WMS-R Digit Span Forward & Block Forward; WCST.	Response ≥ 50% improvement on HDRS following 4 weeks of treatment. Remission ≤ 10 on HDRS at discharge.	Non-responders and patients who failed to achieve remission prior to discharge were specifically impaired in divided attention at baseline.

(Continued)

TABLE 1 | Continued

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
(38)	25 MDD 13 HC	32.5 (11.5)	HDRS-17: 21.3 (4.5) MDRS: 29.4 (4.7)	Naturalistic study. Mixed antidepressant treatment and patients followed up 2–6 months after initial assessment.	Digit Symbol Substitution Test; RAVLT; Paired Associates Learning; Pattern Recognition; Spatial Recognition; Delayed Matching to Sample; COWAT; 'Exclude Letter' Fluency Test; Spatial Working Memory; Tower of London.	Remission defined as HDRS-17 < 8 at follow-up.	At baseline, significantly less psychomotor dysfunction (Digit Symbol Substitution Test) was evident in those who remitted during the follow up period, than those who did not.
(39)	27 MDE, 2 BD-D, 3 BD-NOS	42.2	HDRS: 21.85	3-month open label SSRI trial	Finger Tapping; Stroop; WAIS Digit Symbol; TMT-A, B & B-A; Continuous Performance Test; Buschke Selective Reminding Test; N-Back; A not B Reasoning Test; Letter & Category Fluency; WCST.	Response = ≥ 50% reduction on HDRS24	Responders were significantly better than non-responders on measures of executive functioning, verbal fluency and working memory. Specifically, non-responders were impaired on A not B, N-Back, Letter Fluency and TMT B-A.
(40)	48 MDD	37.96 (10.63)	HDRS-17: 28.25 (5.69)	All participants were treated with SSRIs or SNRIs and followed up approximately 3-4 months later.	Donders Computerized Simple Reaction Time, WMS-R Digit Span; California Verbal Learning Test; Prospective Memory Test; SCWT, Shortened-WCST; COWAT; Modified Six Elements Test.	Remission = at least 50% improvement on HDRS-17 and no longer meeting syndromal criteria.	S-WCST perseverative errors significantly predicted HDRS at follow-up. S-WCST errors and Prospective Memory categories predicted psychosocial outcome (Social and Occupational Functioning Assessment Scale); worse performance predicted poorer outcomes.
(41)	25 MDD	42.8 (14.2)	HDRS-17: 20.2	Open label, non-randomized design. 8 weeks antidepressant treatment-mixed.	IntegNeuro Battery: Motor Tapping Test, Choice Reaction Time Test, Memory Recall & Recognition Test, Maze Task, Letter Fluency, Spot the Real Word Task, Span of Visual Memory Task, Switching of Attention Test, Time Estimation Task, Sustained Attention Task, Digit Span Task, Word Interference Task.	No criteria-primary outcome change in HDRS following 8 weeks of antidepressant treatment.	Linear regression showed that total memory score was significant predictor in model. Higher pre-treatment memory was associated with greater decrease in depressive symptoms.
(42)	86 MDD 55 HCs	44.12 (12.39)	HDRS-21: 22.31 (6.56)	8-week pharmacotherapy - SSRI.	TMT and SCWT	Response ≥ 50% reduction on HDRS Remission < 7 on HDRS	Lower performance in SCWT and TMT-A at admission associated with highest level of depression at end treatment.
(43)	70 depressed patients (41 MDD, 10 dysthymia and 19 both). 57 HCs	SSRI/dual: *R* = 40.2 (11.9) *NR* = 44.1 (14.4) Bupropion: *R* = 40.3 (13.1) *NR* = 39.2 (14.1) HCs = 35.1 (9.8)	HDRS-17: SSRI/dual: *R* = 15.7 (4.4) *NR* = 16.7 (3.9) Bupropion: *R* = 15.8 (3.2) *NR* = 17.2 (4.1)	8–12 weeks of pharmacotherapy treatment-mixed.	COWAT, WAIS Digit Symbol, 4 Choice Reaction Time and SCWT.	Response - HDRS-17 scores reduced by ≥ 50%.	Non-responders to a SSRI or dual therapy showed poorer word fluency than responders, not seen with Bupropion. Longer choice reaction time was also found in non-responders to a SSRI or dual therapy, but the opposite trend was seen for Bupropion. Using a combined index of fluency and reaction time, equal to or above normal, predicted response to a SSRI or dual therapy. In contrast, less than normal performance predicted response to Bupropion alone.

(Continued)

TABLE 1 | Continued

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
(44)	19 melancholic depression 50 atypical depression 35 undifferentiated MDD 200 HCs	MDD: Melancholic-35.1 (13.4) Atypical-32.4 (12.8) Undifferentiated-33.6 (11.7) HC-33.5 (10.1)	HDRS-17: Melancholic-28.2 (5.9) Atypical-26.0 (5.5) Undifferentiated-25.1 (6.9)	6-week open label trial. "Semi-naturalistic" as respective psychiatrist could select antidepressant and dosage.	TMT A & B; WAIS Digit Symbol Substitution, Digit Span; modified-WCST; Tower of Hanoi; Animal Naming; Immediate Visual Reproduction.	No criteria - Looked at change in HDRS-17 from baseline to end treatment (6 weeks).	No cognitive predictors of HDRS after 6 weeks of treatment.
(45)	36 MDD	35.89 (11.71)	HDRS: 19.22 (3.46)	10-week open label trial of either Escitalopram or Duloxetine	Parametric Go/No-Go Test	% Change in HDRS	More commission errors on the Go/No-Go task predicted better treatment response.
(46)	49 MDD	74.8 (5.6)	HDRS-21: 22.5 Cornell Scale for Depression in Dementia: 18.6	6-week antidepressant treatment - various	Psychomotor retardation measure of HDRS and Initiation/Perseveration sub-score of MDRS.	Remission = Cornell Scale score of less than 7.	Abnormal I/P scores and psychomotor retardation predicted change in depression scores 6 weeks following treatment. Non-remitters had poorer I/P scores than remitters.
(47)	110 MDD	73.78	MADRS: 24.65	Standardized treatment algorithm-3 months of antidepressant treatment & ECT.	TMT A & B; COWAT; Category Fluency; Benton Visual Retention Test; WAIS-R Digit Span.	Remission = MADRS score of less than 7.	Those who remitted had significantly fewer perseverative errors on COWAT and better performance on Digit Span Forward, than non-remitters.
(48)	100 MDD	69.1 (6.9)	MADRS: 21.8 (8.2)	Assessment of depression and cognitive functioning at study entry and 1 year follow up. Pharmacological treatment with STAGED approach.	TMT A & B; Symbol Digit Modalities Test; WMS-R Logical Memory; Recall of Words from Consortium to Establish a Registry of Alzheimer's disease Word-list.	High response defined as MADRS rating change greater than baseline standard deviation of the sample.	High response individuals (1 year) demonstrated better: baseline Logical Memory delayed recall, Logical Memory % retention, Delayed Word-list recall and higher SDMT scores. Poor baseline performance on tests of verbal memory and processing speed associated with reduced treatment response.
(49)	142 psychotic MDD	71.7 (7.8)	HDRS-17: 30.1 (5.4)	12-week double blind RCT of Olanzapine + Sertraline or Olanzapine + placebo	SCWT and Initiation/Perseveration subscale of MDRS.	No criteria. Conducted a series of linear regressions, with executive function and processing speed as the independent variables and change in HDRS-17 as the outcome variable.	Neither executive functioning nor processing speed predicted change in depression scores.

BACS, Brief Assessment of Cognition in Schizophrenia; BDI, Beck Depression Inventory; BD-D, bipolar disorder–depressed; BD-NOS, bipolar disorder not otherwise specified; CGI, Clinical Global Impression Scale; COWAT, Controlled Oral Word Association Test; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; Fourth Edition, ES, effect size; HC, healthy control; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MCCB, MATRICS Consensus Cognitive Battery; MDD, major depressive disorder; MDE, major depressive episode; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; NR, non-responder; QIDS, Quick Inventory of Depressive Symptomatology; R, responder; RAVLT, Rey Auditory-Verbal Learning Test; RVIP, Rapid Visual Information Processing; SCWT, Stroop Color and Word Test; SNRI, Serotonin Noradrenaline Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; STAGED, Somatic Treatment Algorithm for Geriatric Depression; TMT, Trail Making Test; WAIS-R, Wechsler Adult Intelligence Scale; Revised, WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale-Revised.

TABLE 2 | Reviewed studies using other treatments during the follow-up period.

Study	N	Age (SD)	Depression severity	Study design	Cognitive tests	Response/remission criteria	Key outcomes
(50)	19 MDD	37.2	HDRS: 26	3-week, randomized trial of CBT or CBT + Sleep deprivation therapy.	D2 Letter Cancellation Test, Test of Attentional Performance, Zahlen Verbindings Test, subtest 6 of German Intelligence Battery, German version of Auditory Verbal Learning Test.	No criteria-primary outcome post treatment HDRS.	For the CBT only group, declarative verbal memory and word fluency predicted clinical response (percentage improvement on HDRS).
(51)	57 MDE	46.7 (11.6)	MADRS: 29.4 (5.4)	Data pooled from 5 clinical trials of transcranial direct current stimulation-2 double-blind (10 and 15 sessions) and 3 open-label (20 sessions).	RAVLT; Digit Span, COWAT; Symbol Digit Modalities Test; Simple & Choice Reaction Time.	No criteria-primary outcome post-treatment MADRS.	Better pre-treatment performance on COWAT associated with better antidepressant response to transcranial direct current stimulation.
(25)	Details in **Table 1**						
(52)	20 TRD	47.4	HDRS-17: 24.3	12 months of subcallosal cingulate gyrus deep brain stimulation.	WCST, Hopkins Verbal Learning Test, COWAT, Finger Tap Test, Stroop.	Response-HDRS scores reduced by ≥ 50.	Dominant-hand finger tap test and WCST-Total errors predicted treatment response with a high degree of accuracy. Responders performed significantly better on the finger tapping test, but had significantly more errors on the WCST.
(49)	25 MDD	70.80 (5.52)	HDRS-17: 30.19 (5.76)	12-week antidepressant treatment regimen within a 12-month follow-up period. ECT was the final treatment option, with 48% receiving ECT treatment.	WAIS Block Design, Digit Span (forward and backward), Digit Symbol subtests; WMS Logical Memory and Visual Memory subtests; TMT-A; Tower of London.	Remission was defined as a 17-item HDRS score below 8 between the 6-month and the 12-month visit.	A quantitatively similar performance (whether high, average or low) on verbal learning (Visual Memory associative learning) and planning (Tower of London) appeared to predict remission.
(53)	46 MDD	70.78 (7.3)	HDRS-25: 22.54 (2.7)	12-week randomized trial of problem solving therapy or supportive therapy.	Hopkins Verbal Learning Test; WCST; TMT A & B; COWAT, Animal Naming.	Response - HDRS scores reduced by ≥ 50. Remission-post-treatment HDRS score ≤ 10.	Worse performance using empirically derived cut-off score of ≥ 82 on TMT-B, detected 59.6% of psychotherapy treatment responders. Suggests poor baseline switching ability may predict treatment response.
(54)	11 TRD	74.1 (7.81)	MADRS: 25.7 (7.3)	4-week open trial of cognitive remediation (30 h).	TMT A & B; MDRS Initiation/Perseveration subscale; California Verbal Learning Test; WAIS IV Digit Backward.	No criteria - primary outcome change in MADRS.	Higher TMT B - A scores (indicative of greater executive dysfunction) associated with greater reduction in MADRS scores following 4 weeks of cognitive remediation.

CBT, cognitive behavior therapy; CGI, Clinical Global Impression Scale; COWAT, Controlled Oral Word Association Test; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; MDRS, Mattis Dementia Rating Scale; RAVLT, Rey Auditory-Verbal Learning Test; TMT, Trail Making Test; TRD, treatment resistant depression; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WMS, Wechsler Memory Scale.

to note that the way in which tests have been categorized in this review may not align with the cognitive domains described in the original studies; however, it was imperative to organize tests in a standardized way. Given there is considerable overlap in tasks assessing executive function and attention, it was decided to combine both of these cognitive functions together. Further, although working memory is sometimes classified under learning and memory, in this review, it has been classified under the umbrella term of executive functioning. For the purposes of this review, samples containing participants ranging from 18 to 65 years will be referred to as adult samples, and those containing individuals aged 65 and above, will be referred to as older-aged samples.

Single Antidepressant Trials

Executive Function/Attention

Eleven studies examined the relationship between executive function/attention and treatment outcomes in 13 adult samples receiving antidepressant monotherapy. Four shorter treatment trials (five samples), examined predictors of response to selective serotonin reuptake inhibitors (SSRIs). Three samples showed an association between poorer executive function/attention performance and poor overall treatment response (total $n = 268$) (13, 14, 20). Conversely, two samples showed no evidence of an association (total $n = 306$) (17, 20). Etkin et al. (20) examined predictors of response to Escitalopram ($n = 217$) and Sertraline ($n = 234$). They found that impairment in attention and working memory was associated with non-remission on Escitalopram; however, this relationship was not seen with Sertraline (20). Of the negative studies, Gudayol- Ferré et al. found no evidence of an association between executive function or attention and overall response to Fluoxetine (17); however, they did find an association with early treatment response and time to remission (16, 18). In their sample of 72 depressed patients, poorer attention and spatial working memory were associated with poorer response at 4 weeks, but the opposite relationship was seen with "subsequent thinking time" on the Stockings of Cambridge (16). Additionally, the authors also found that those with poorer spatial working memory performance were slower to remit at treatment-end; thus, their findings with respect to attention and spatial working memory are in line with the other positive studies (18).

In a longer treatment trial, Bastos et al. (25) examined the relationship between executive function performance and response to 24 months of treatment with Fluoxetine ($n = 91$), psychodynamic psychotherapy ($n = 90$) or a combination thereof ($n = 90$). The largely negative results were complex. Of 14 cognitive variables, higher scores on two (WAIS-III, Letter Number Sequencing and Matrix Reasoning) were associated with better response across all three treatments (Fluoxetine, psychodynamic psychotherapy and the combination) and higher scores on one (WAIS-III, Similarities) was associated with poorer response (25).

Whilst one small study has found an association between poorer executive function/attention performance and poor response to SNRIs ($n = 25$) (21), a much larger study has found no evidence of a relationship ($n = 204$) (20).

In a naturalistic multi-center trial of 6–8 weeks of Agomelatine (an antidepressant with a primarily melatonergic action) treatment ($n = 508$), the number of omissions on the D2 Cancellation Task (a measure of attention) predicted clinical and functional remission in patients with moderate to severe depression. Moreover, a dose-response relationship was observed, whereby treatment outcomes were increasingly more positive as less omission errors were made on the task (24).

One study has examined the relationship between baseline executive measures and response to the combined dopamine and noradrenaline re-uptake inhibitor, Bupropion. Herrera-Guzmán et al. ($n = 26$) found that poorer performance on the Stockings of Cambridge at baseline predicted poorer response to 8 weeks of Bupropion treatment (15).

Three studies have examined cognitive predictors of Ketamine response, with two (total $n = 38$) finding evidence of an association between poorer executive function/attention performance and better treatment response (19, 22). Murrough et al. (22) ($n = 25$) found that responders to a single infusion of Ketamine Hydrochloride performed significantly worse on tests assessing working memory, than non-responders (22). In line with this finding, Shiroma et al. (19) found that the likelihood of responding to six infusions of Ketamine was greater in those who demonstrated poorer attentional abilities at baseline (19). In contrast, a second study by Murrough et al. ($n = 43$), showed no association between executive function/attention performance and treatment response (23).

Seven studies examined the relationship between executive function/attention and treatment-related outcomes in response to antidepressant (SSRI) monotherapy in older-aged samples. Five of the studies found that deficits in executive functioning were associated with poor remission rates/antidepressant response (combined $n = 341$) (26, 28, 29, 32, 34, 35). In contrast, one small study ($n = 12$) found no difference in executive function performance between remitters and non-remitters (30). One study ($n = 13$) examined the relationship between executive function/attention and time to remission and found that individuals with impaired executive functioning, as shown by greater conflict scores on the Attention Network Test, took longer to remit (31).

Psychomotor Speed

Ten studies examined the relationship between psychomotor speed and response to antidepressant monotherapy, in 12 adult samples. Four shorter treatment trials examined predictors of response to SSRIs. In two samples (14, 20), slower psychomotor speed was associated with poorer response to treatment (total $n = 254$). In contrast, three samples showed no association between SSRI treatment and psychomotor speed ($n = 320$) (13, 17, 20). In the large study by Etkin et al. slower psychomotor speed was associated with non-remission to Escitalopram, but not to Sertraline (20). One study examined the relationship between psychomotor speed and 24 months of treatment with an SSRI (25). The study found that slower psychomotor speed was associated with poorer response to Fluoxetine treatment ($n = 91$).

No association was found between psychomotor speed and response to SNRIs ($n = 204$) (20), Bupropion ($n = 26$) (15) and

Agomelatine ($n = 508$) (24). Two studies (total $n = 68$) (22, 23) examining the relationship between psychomotor speed and response to Ketamine found that slower psychomotor speed at baseline predicted greater improvement in depressive symptoms following treatment. Conversely, one Ketamine study ($n = 13$) found no association (19).

Three studies have examined the relationship between psychomotor speed and overall treatment response in older-aged adults. None of the studies (total $n = 594$) found an association between psychomotor speed and treatment response (27, 33, 34). However, one study ($n = 84$) did find that slower psychomotor speed was associated with slower response to treatment. Sneed et al. (33) found that individuals with slower psychomotor speed took longer to respond to Citalopram than those with faster psychomotor speed; however, by the end of treatment (week 8), both groups were equal in their level of response (33).

Verbal Learning and Memory

Eight studies examined the relationship between verbal learning and memory, and treatment-related outcomes in response to antidepressant monotherapy in adult samples. Seven shorter treatment trials (total $n = 885$) (13, 15, 17, 19, 22, 23), plus one long-term treatment trial ($n = 91$) (25), found no evidence of an association between the two. Likewise, the four studies that examined verbal learning and memory in older-aged samples (total $n = 616$) found no relationship between verbal learning and memory performance and treatment-related outcomes (26, 27, 33, 34).

Non-verbal Learning and Memory

Seven studies examined the relationship between non-verbal learning and memory performance and treatment-related outcomes in response to antidepressant monotherapy in adult samples. Six shorter studies (total $n = 204$) (13, 14, 17, 19, 22, 23) and one longer-term study ($n = 91$) (25) found no relationship between non-verbal learning and memory, and treatment response. One study ($n = 26$) found that poorer non-verbal memory performance was associated with better response to a combined dopamine and noradrenaline re-uptake inhibitor (26). In their 8-week trial of Bupropion, Herrera-Guzmán et al. found that responders performed significantly worse on a measure of visual memory (Paired Associates Learning) than non-responders (15). One study has examined the association between non-verbal learning and treatment response in older-aged depression ($n = 22$); however, they found no evidence of a relationship between the two (26).

Emotional Processing

Only two studies have examined the predictive nature of emotional processing in relation to treatment response in depression. In a younger adult sample, Etkin et al. (20) found that slower emotion identification speed was associated with non-remission to Escitalopram ($n = 217$), but not Sertraline ($n = 234$) or Venlafaxine ($n = 204$) (20). In an older-aged sample ($n = 12$), Alexopoulos et al. (30) found no differences between remitters and non-remitters in terms of their performance on an emotional go/no-go task following 8 weeks of treatment with Escitalopram (30).

Mixed Antidepressant Treatment

Executive Function/Attention

Ten studies examined the relationship between executive function/attention and response to mixed antidepressant treatment in 11 adult samples with depression. In five of the samples (total $n = 291$), poorer executive function/attention was associated with poorer response to various pharmacological treatments (37, 39, 40, 42, 43). In a sample of particularly severely depressed inpatients, Whithall et al. (40) found that poorer executive function performance was associated with negative clinical and functional outcomes in inpatients treated with SSRIs or SNRIs. More perseverative errors on the shortened Wisconsin Card Sorting Test (WCST) at baseline, was associated with greater depression severity at follow-up. Further, more perseverative errors on the WCST in addition to poorer event-based prospective memory, was associated with poorer social and occupational outcomes in their sample (40). In contrast, one small study ($n = 36$) found the opposite relationship between executive function performance and treatment response. Crane et al. (45) found that more commission errors on the Parametric Go/No-Go test predicted better treatment response to Escitalopram or Duloxetine (45). Four samples (total $n = 228$) showed no association between executive function/attention performance and overall treatment response (36, 38, 41, 43, 44).

Four studies examined the relationship between executive function/attention and treatment response in older-aged samples. Two studies (total $n = 159$) found an association between executive dysfunction and poor treatment response (46, 47). In the largest positive study, Potter et al. (47) ($n = 110$) found that remitters to a standardized treatment algorithm over 3 months had significantly fewer perseverative errors on the Controlled Oral Word Association Task (COWAT) and better performance on Digit Span Forward, than non-remitters (47). Story et al. (48) ($n = 177$) examined response to a standardized treatment algorithm over one year and found no association with executive function performance (48). Additionally, in a 12-week randomized controlled trial (RCT) comparing Olanzapine plus Sertraline with Olanzapine plus placebo ($n = 142$), Bingham et al. (49) found no association between baseline executive functioning and depression scores post treatment (49). This study did not present data separately for the two treatment groups.

Psychomotor Speed

Eight studies examined the relationship between psychomotor speed and treatment outcomes with mixed antidepressant treatment in nine adult samples. Three samples (total $n = 159$) showed an association between slower psychomotor speed and poorer response to treatment (38, 42, 43). In the largest positive study ($n = 86$), slower performance on Part A of the Trail Making Test (TMT) was associated with greater depressive symptomatology following 8 weeks of SSRI treatment in a sample of adults with severe depression (42). In contrast, six samples (total $n = 283$) showed no association between psychomotor

speed and treatment response (39, 41, 43, 44). In a sample of 104 individuals with depression, Lin et al. (44) found no association between psychomotor speed and improvement in HDRS scores following 6 weeks of treatment (44).

Four studies examined the relationship between psychomotor speed and treatment response in older-aged samples. One 6-week study ($n = 49$) and one 12-month study ($n = 177$) found an association between poorer psychomotor speed and poor treatment response (46, 48), whilst two studies ($n = 252$) did not (47). In the larger positive study ($n = 177$), Story et al. (48) found that depressed older persons with better baseline performance on the Symbol Digit Modalities Test, showed the greatest improvement in depressive symptomatology at one-year follow-up (48).

Verbal Learning and Memory

Five studies have examined the predictive value of verbal learning and memory in relation to mixed antidepressant treatment in adult samples. Spronk et al. (41) found that higher pre-treatment verbal memory performance was associated with a greater reduction in depressive symptoms, in a sample of 25 individuals with major depressive disorder (MDD) (41). Four other studies found no association between verbal memory and treatment response (total $n = 157$) (38–40).

Two studies have examined the relationship between verbal learning and memory, and treatment response in older-aged adults. Story et al. (48) ($n = 177$) found that depressed older adults who performed well on verbal memory tasks prior to being treated with a stepped approach, showed the greatest improvement in depressive symptomatology at 1-year follow-up (48). However, another study ($n = 110$) found no relationship at 3-month follow-up (47).

Non-verbal Learning and Memory

Three studies examined the relationship between non-verbal learning and memory and treatment outcomes with mixed antidepressant treatment in adults (38, 44), and none of the studies found evidence that non-verbal learning and memory predicts treatment response (total $n = 181$). Likewise, the single study that examined non-verbal learning and memory in older-aged samples found no association between the two ($n = 110$) (47).

Emotional Processing

Only one study has examined the relationship between emotional processing and treatment outcomes with mixed antidepressant treatment in adults with depression. In the study by de Groot et al. (36), there was no significant difference between responders and non-responders in terms of their performance on a facial expression recognition task at baseline (36).

Other Biological Treatments

Two studies have examined cognitive predictors (executive function, verbal learning and memory, and psychomotor speed) of treatment response to other biological treatments in younger adult populations. Martin et al. (51) pooled data (total sample, $n = 57$) from five clinical trials of anodal transcranial direct current stimulation and found that better baseline performance on the COWAT (a measure of executive functioning), was associated with better response to transcranial stimulation (51). McInerney et al. (52) examined cognitive predictors of 12 months of subcallosal cingulate gyrus deep brain stimulation ($n = 20$) and found that better psychomotor speed, but greater executive dysfunction, predicted better response to treatment (52).

One study examined cognitive predictors of treatment response to other biological treatments in older-aged individuals. Marcos et al. (55) assessed the predictive value of executive functioning/attention, verbal learning and memory, non-verbal learning and memory, and psychomotor speed, in a 12-week antidepressant trial ($n = 25$). ECT was available if patients failed to respond to pharmacological treatment, with 48% of the sample receiving ECT at some point during the trial. The authors found no association between cognitive function and response to treatment (55).

Psychosocial Treatments

Two studies have examined cognitive predictors of psychosocial treatment response in adults with depression (25, 50). Kundermann (50) examined the predictive value of executive function/attention, verbal learning and memory and psychomotor speed, in a 3-week trial of Cognitive Behavior Therapy (CBT) vs. CBT + sleep deprivation therapy ($n = 19$). The authors found that better verbal fluency and declarative verbal memory were associated with better clinical response (percentage improvement on the HDRS) in those receiving CBT alone. However, this relationship was not seen in the group receiving CBT + sleep deprivation therapy. No association was found between psychomotor speed and treatment response in either of the two groups (50).

Bastos et al. (25) examined the relationship between executive function, verbal learning and memory, and processing speed, and response to 24 months of psychodynamic therapy ($n = 90$), Fluoxetine ($n = 91$) or psychodynamic therapy with adjunctive Fluoxetine treatment ($n = 90$). The authors found mixed findings in relation to the predictive value of executive functioning. Across all three treatment groups, better Letter-Number Sequencing and Matrix Reasoning scores, predicted lower depression symptoms (BDI) at 24 months. Conversely, better Similarities scores were associated with greater depression symptoms following treatment. The authors also found that in those receiving psychodynamic therapy or both treatments combined, better Digit-Symbol Coding scores (i.e., faster psychomotor speed) were associated with greater depression severity at follow-up (25).

Two studies have examined the association between cognitive function and response to psychotherapy in older-aged samples with depression (53, 54). Both examined executive functioning/attention, verbal learning and memory, and psychomotor speed. Both studies found executive functioning to be the only domain associated with treatment-related outcomes. Beaudreau et al. (53) ($n = 46$) found that poor baseline performance on Part B of the TMT (a measure of cognitive flexibility), detected 59.6% of individuals who responded to 12 weeks of either problem-solving therapy or supportive therapy. In a 4-week trial of cognitive remediation, Morimoto et al. (54)

found that higher TMT B-TMT A scores (indicative of greater executive dysfunction) was associated with greater reduction in Montgomery-Asberg Depression Rating Scale (MADRS) scores following treatment (54).

DISCUSSION

Summary of Results

Since different treatments may act differently on brain circuitry and there is evidence that modulation of specific receptors or circuits may differentially affect cognitive function, it is important in the first instance to divide the results of the review into studies examining response to different treatment modalities. In addition, whilst this review excluded studies that included patients with likely onset of dementia (MMSE <24), changes associated with aging, multiple episodes of depression or late onset depression may result in a different pattern of association in older samples. Therefore, we have separated the results into adult and older-aged samples. In summary, the results are as follows:

Executive Function/Attention

There was some consistency in findings from studies examining response to SSRIs in adult samples. Three samples treated with a single SSRI (13, 14, 20) (total $n = 268$) and two samples openly treated with any SSRI ($n = 123$) (39, 42) showed that reduced executive function was associated with poorer response. In contrast, two single SSRI studies (total $n = 306$) showed no association (17, 20). In older-aged samples, the findings were much more consistent. Five studies showed an association between executive function and overall response to SSRIs (total $n = 341$) (26, 28, 29, 32, 34, 35), and one found an association between executive function performance and time to remission (31). Only one small study ($n = 12$) found no differences in executive functioning between remitters and non-remitters (30).

In terms of other agents, one large study found that poorer attention was associated with poorer response to a melatonergic agent in an adult sample ($n = 508$) (24). There was limited, or no evidence, of an association between executive function/attention and response to SNRIs, Bupropion, Ketamine, ECT or psychosocial treatments.

Psychomotor Speed

There was some evidence of a relationship between psychomotor function and response to SSRIs in adult samples. Two samples (total $n = 254$) showed that slower psychomotor speed was associated with poorer response (14, 20). Additionally, one longer-term SSRI study ($n = 91$) (25) and one sample openly treated with any SSRI ($n = 86$) (42), showed the same association. In contrast, three adult samples ($n = 320$) treated with a single SSRI (13, 17, 20) and one sample openly treated with any SSRI (39), showed no association. There was no association in older-aged adults.

There was limited, or no evidence, of an association between psychomotor speed and response to SNRIs, Bupropion, Ketamine, Agomelatine, ECT or psychosocial treatments in adult or older-aged samples.

Learning and Memory

There was limited evidence of a relationship between learning and memory (verbal or non-verbal) and treatment response in adult or older-aged samples.

Prediction of Response to Monoamine Reuptake Inhibitors

As noted in the summary above, the data in younger participants is dominated by the large study of Etkin et al. (20). The sample randomly assigned to Escitalopram showed that executive dysfunction was associated with poorer response, while there was no such association for the other SSRI, Sertraline (20). The authors speculated that the difference between Escitalopram and Sertraline may relate to the exact pharmacodynamic properties of the agents, the suggestion being that Escitalopram is a more specific SSRI while Sertraline has more noradrenergic and dopaminergic reuptake inhibition. The other related possibility is that their findings were related to dose; however, the validity of such explanations is not clear. The doses of all three antidepressants in the international Study to Predict Optimized Treatment in Depression (iSPOT) study were low (Escitalopram 12 mg, Sertraline 62 mg, Venlafaxine 83 mg) (56). Evidence does not suggest that Venlafaxine has significant effects on noradrenaline re-uptake at this dose (57, 58). *In vitro*, Sertraline has been shown to inhibit noradrenaline and dopamine reuptake (59), but the extent to which this occurs at the doses used in this study *in vivo* is unclear. Furthermore, neither of these factors can explain the differential response whereby those with poorer cognitive function were more likely to remit with Sertraline/Venlafaxine and those with better cognitive function were more likely to remit with Escitalopram. In the iSPOT study, and in meta-analyses, there was no difference in overall efficacy between these three antidepressants (56, 60). The analysis used in this study was different from that used in all other studies, using a cross-validated multivariate pattern classification approach. This allows different variables to be weighted differentially in order to obtain the best predictive model. As such, it is significantly different from the simpler methods of examining association and less comparable than the results from other studies.

Results for processing speed are similar to those for executive function, with the largest study showing a relationship between processing speed and response to treatment with Escitalopram but not Sertraline or Venlafaxine (20). It has been suggested that reduced psychomotor function indicates a particular subtype of depression; melancholic depression (61). Further, it is suggested that this responds preferentially to dual action drugs compared with SSRIs or psychotherapy (62, 63). The association with response to Escitalopram but not Venlafaxine could therefore relate to a poor response of "melancholic" patients—in this context indicated by psychomotor impairment—to Escitalopram but not Venlafaxine. However, as noted, Venlafaxine at this dose may vary little from a standard SSRI. It has been suggested that measuring psychomotor function either by testing or observation, is a better way of assessing a measurably different ("melancholic") group.

Response to Other Agents and Biological Treatments

A large study examining predictors of response to Agomelatine (an antidepressant with a primarily melatonergic action), showed that those who performed better on an attentional task were more likely to achieve both clinical and functional remission (24). The authors postulated that the ability to direct attentional resources toward, and away from, emotionally-laden stimuli, is critical for effective emotional regulation. Thus, attentional deficits would likely impact one's ability to regulate emotion; thereby, contributing to persistent negative affect (24).

Interestingly, studies examining Ketamine found the opposite relationship between cognitive functioning and treatment response, with poorer neurocognitive performance, particularly slower psychomotor speed, predicting greater improvement in depressive symptoms (19, 22, 23). While preliminary, the findings suggest that responders to Ketamine may show a distinct cognitive profile compared with those who respond to other types of antidepressants, such as SSRIs. Dopaminergic transmission within prefrontal-subcortical circuits has been implicated in several cognitive processes, including psychomotor function (64); further, Ketamine has been shown to modulate dopamine transmission within these brain regions (65, 66). Although Ketamine's exact mechanism of action is yet to be fully elucidated, it is possible that its antidepressant effects are through modulation of dopaminergic signaling. In line with this, Bupropion is a relatively specific dopamine and noradrenaline reuptake inhibitor, and Herrera-Guzmán et al. (15) found that poorer executive function performance predicted better response to Bupropion ($n = 26$).

Response to Psychotherapy

Few studies have examined cognitive predictors of response to psychotherapy. Focusing on the short-term studies, one study found that better executive functioning and verbal memory were associated with better response to treatment with CBT (50). Conversely, two studies found that executive dysfunction predicted better response to Problem Solving Therapy (PST) and supportive therapy (67), and cognitive remediation (54). The discrepancy in findings may be due to the nature of the psychosocial treatments being used. The latter studies incorporated treatments that either targeted executive dysfunction and its underlying pathophysiology (PST and cognitive remediation) or did not rely heavily on executive processes (supportive therapy). Therefore, it is possible that treatments which support or improve executive functioning, may facilitate clinical improvement in those experiencing such cognitive deficits.

Data in Older-Age Samples

Particularly for executive function, data in older-age samples are remarkably consistent. Most studies showed that impaired executive function was associated with poorer response to treatment. It is possible that this may be related to the number of previous episodes, as both cognitive functioning and treatment response decline with increasing depressive episodes (68, 69). Some authors have suggested that executive dysfunction is particularly prominent in the older-age individuals (70), although not all studies have agreed (71). If executive function is particularly prominent or frequent in these samples, then this would reduce the likely dilution effect of including patients with minimal deficit. One large study which illustrates this effect was excluded from this review based on their use of a different measure of response (functional measure) (12). A treatment specifically designed to counteract the negative prognostic effect of executive deficit, Problem Solving Therapy (PST), was compared with supportive therapy in a sample of old-age depressed patients. An advantage was seen for PST, particularly in those patients with greater executive deficit. This study is unique because it is enriched specifically for executive impairment. It therefore addresses an issue which is particularly important in this area—the dilution of findings by inclusion of patients without cognitive impairment (72).

Neurobiological Underpinnings

As mentioned above, there appears to be some support for the notion that executive dysfunction can predict treatment-related outcomes, particularly in the elderly depressed; with deficits in executive functioning/attention predicting poorer or slower response to treatment. One reason for this finding may be that impaired executive function performance serves as a marker for dysfunction within the fronto-limbic circuits. Executive functioning is sub-served by areas within the prefrontal cortex and there is consistent evidence that depression is associated with aberrant neural activity in these brain regions (73, 74). It has been proposed that reduced prefrontal control over limbic activity leads to impaired emotional regulation and maladaptive thinking patterns, such as rumination and worry, all of which are believed to contribute to the development and maintenance of depression (75, 76). Thus, poor performance on executive function tasks may highlight key pathological processes that serve to not only maintain depression but preclude response to treatment.

Methodological Issues

Although not an exhaustive list, the following section will discuss the most pertinent methodological considerations related to the studies included in the current review.

1. Standardized monotherapy vs. open label trials and algorithm-based treatment—We have dealt with the results based on the treatment used. It is important to note that there is a fundamental difference between a trial of a single agent and one which allows changes in treatment based on tolerance and response. In monotherapy, for example, patients may not respond because they cannot tolerate the treatment; something which is unlikely to be directly related to cognitive function. In contrast, open and algorithm-based treatment trials permit changes to treatment if an agent is not tolerated, and the patient may still be classified as a responder. These trials have greater ecological validity and may more accurately reflect the clinical implications of cognitive impairment in determining real-life response. However, they do not give accurate information regarding likelihood of response to one agent compared with another.

2. Length of trial–There is a marked difference between the timing of the clinical outcome between trials (in this review ranging from 24 h to 1 year). On one hand, a short outcome may constrain the time available to respond, making differentiation between patients less likely. However, longer outcome times (e.g., 1 year) allow various other factors to operate, thereby reducing the likelihood of finding a clear association. For example, patients in such studies may respond and then relapse within the time frame of the study. In older-age samples, a longer outcome may also involve development or progression of a neurodegenerative process, meaning that cognitive impairment is in fact associated with further cognitive decline.
3. Choice of outcome measure–Trials have used a variety of ways of measuring response, including percentage reduction in mood rating scale scores, rates of response and rates of remission. The former keeps response on a dimension and is likely to be more sensitive than a binary outcome. Especially in short trials, remission is relatively infrequent and reduces the sensitivity of the analysis; however, it is the optimal and arguably most clinically-relevant outcome. Another related issue is the utilization of multiple outcome measures. This increases the number of comparisons being made and the likelihood that an association may be purely due to chance.
4. Severity of depression at baseline–There are several issues regarding depression severity at baseline. Firstly, placebo response tends to be greater in milder depression, possibly indicating less of a biological basis (77). Response in this case is less likely to be biologically determined and therefore, less likely to be influenced by cognitive impairment. Secondly, a related issue is that in mild to moderate depression, the percentage of patients who have cognitive impairment is relatively low (78); hence, using such a sample will likely dilute findings (see below). Thirdly, in milder depression, the range of possible change on depression rating scales is smaller, which ultimately reduces the likelihood of finding an association between baseline cognitive functioning and change in depressive symptomatology.

   A related issue is the way in which severity of depression has been accounted for in the analysis of the relationship between cognitive variables and outcome. This is clearly important since the relationship between cognitive function and outcome may be mediated wholly or partly by severity of depression. Most large studies accounted for this by some form of covariate analysis. Other studies simply compared the baseline depression rating score of responders compared with non-responders, and if this was not significantly different, concluded that this was not an important mediator of difference in cognitive function. Clearly, this issue should be addressed in future research.
5. Degree of cognitive impairment at baseline–It is less likely that cognitive function will be associated with outcome in patients whom are not classed as "cognitively impaired." Having such patients in a study will dilute findings, potentially to the point of a genuine association not being demonstrated. Some of the reviewed studies had control participants and indeed found a difference between controls and the group overall (20, 79), but this does not mean that all, or even a high percentage of patients, were impaired (78). It is likely that studies including more severely unwell patients have a higher percentage of patients with significant cognitive impairment and are therefore, more likely to show an association with response. In the study of Etkin et al. (20), the importance of this phenomenon is illustrated, with the predictive effect of cognitive performance only applied in the group who, compared with healthy controls, were significantly impaired.
6. Cognitive battery–Studies using a more extensive battery of cognitive tasks may be more likely to show an association with response simply because they have used multiple tests, and an association with one of these may simply be a feature of multiple comparisons. However, it could be argued that certain aspects of, for example executive function, may be more likely to affect response than others. Pimontel et al. (80), in a meta-analysis of executive function tasks in the elderly, conclude that only planning and organization (as measured by a subtest of the Dementia Rating Scale) was associated with response. Using composite scores for each domain may reduce the problem of multiple comparisons, but as noted, some may argue that this neglects individual aspects of cognitive functioning. Very short batteries may measure cognitive domains inadequately and result in false negative findings. Additionally, cognitive tasks themselves may vary in their sensitivity and suffer from ceiling effects. For example, the Hopkins Verbal Learning Test may not measure verbal learning and memory with adequate sensitivity, and even the Rey Auditory Verbal Learning Test may be subject to ceiling effects; thus, more sensitive tasks are needed (81).
7. Classification of drop-outs–Outcome can be analyzed either by intention-to-treat or using only completers. Most studies in the review classified patients as responders or remitters based on pre-defined criteria and classified drop-outs as non-responders/remitters. A small number, including one of the largest studies in the review (20), examined change in depression rating scale scores and therefore included in the analysis only patients who completed follow-up rating scales. However, they also undertook an intention-to-treat analysis and a sensitivity analysis, showing that the method of analysis made no difference in this case. The advantage of the former is that it includes all patients and gives a potentially more useful clinical result informing what the likely overall outcome is for patients with differing cognitive profiles. However, the relationship between cognitive function and outcome may be altered by the group of patients who are particularly sensitive to side effects which may not relate to cognitive function.

Limitations

There are several limitations of the current review. Firstly, as is usual in English language-based reviews, only peer-reviewed articles in the English language were included, which may have resulted in some useful sources of evidence being missed. Secondly, given the heterogeneity of outcome measures, the variety of treatment protocols, and the differing ways in which data was presented and analyzed, it was not possible to use a meta-analytic technique. This meant that a quantitative

result could not be produced. Thirdly, no formal risk of bias methodology was utilized in the present review (e.g., Cochrane risk of bias tool). However, differences in assessment were discussed between the three co-authors and studies of greater quality were given greater weight in synthesizing the evidence. Further, methodological issues related to the reviewed studies are discussed.

Recommendations for Future Research

1. Studies examining this issue will have low yield unless they have a significant proportion of patients with significant cognitive impairment. Selection of patients may require a strategy to enrich samples, or simply to recruit more severely depressed samples.
2. The issue of chance findings is important. We suggest that studies employ *a priori* groupings of variables into domains and utilize composite domain scores in analysis. This reduces the number of variables examined. Secondary analyses can examine individual variables to elicit any more specific signals regarding detailed cognitive functions which may be associated with response.
3. The majority of studies have employed outcome measures of response or remission. Although it can be argued that these are more clinically meaningful, examining response on a dimensional scale (i.e., percentage change in mood rating scale scores) is likely to be more sensitive; thereby, increasing the likelihood of detecting an association between cognitive functioning and response. One way to deal with this issue is to be clear regarding which primary outcome is to be related to cognitive function but to report other associations in secondary analyses, thereby making these data easily accessible for meta-analyses, but avoiding the problem of multiple outcomes analyses.
4. It appears that "cold" (i.e., traditional) cognitive functions have been the main focus in this area of research, with only three studies having assessed the predictive nature of emotional processing. There is strong evidence that depressed individuals experience alterations in emotional processing (e.g., negatively interpreting emotionally laden stimuli) (76, 82). Moreover, "hot" (i.e., emotional) cognitive processes are believed to play a role in the development and maintenance of depressive symptoms. Thus, more focus should be placed on assessing the relationship between emotional processing and treatment response.

Summary, Conclusions and Clinical Implications

In younger patients, the data is inconclusive both regarding the association between cognitive function and response to any treatment, and regarding association with response to specific treatments. The best evidence is for a predictive effect of executive function, and with some support for an association with psychomotor function. There is no evidence of learning or memory being associated with treatment response. The main methodological issue we believe is that samples were relatively mildly depressed and therefore, likely contained few patients with significant cognitive impairment. The evidence in older adults is much more consistent and suggests that poor executive function predicts poor response to SSRIs, with little evidence regarding response to other agents. In line with this, one notable study showed that specifically addressing executive dysfunction in the elderly depressed, had positive effects (12).

It is apparent that this area of research is affected by a number of important methodological issues, which need to be addressed in order to help fully elucidate the relationship between cognitive functioning and treatment outcomes in depression. Nevertheless, the findings from the present review do suggest that certain aspects of cognitive functioning, particularly executive function, may be useful in predicting treatment response in depression. This is certainly the case in older-aged samples, with evidence suggesting that executive dysfunction can predict poor response to SSRI treatment. The findings also indicate a possible rationale for specifically targeting cognitive functioning during treatment, as doing so may result in improved treatment outcomes.

AUTHOR CONTRIBUTIONS

SG conducted the systematic review of papers and prepared the first draft of the manuscript. RP and KD supervised the systematic review and reviewed and updated subsequent drafts.

ACKNOWLEDGMENTS

We are grateful to the University of Otago for their financial support by providing SG with a University of Otago Doctoral Scholarship.

REFERENCES

1. GBD 2016. Disease and injury incidence and prevalence collaborators global regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* (2017) 390:1211–59. doi: 10.1016/S0140-6736(17)32154-2
2. Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry* (2007) 164:739–52. doi: 10.1176/ajp.2007.164.5.739
3. Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, et al. STAR*D: revising conventional wisdom. *CNS Drugs* (2009) 23:627–47. doi: 10.2165/00023210-200923080-00001
4. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust New Zealand J Psychiatry* (2015) 49:1087–206. doi: 10.1177/0004867415617657
5. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D., et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

6. Porter RJ, Robinson LJ, Malhi GS, Gallagher P. The neurocognitive profile of mood disorders - a review of the evidence and methodological issues. *Bipolar Disord.* (2015) 17(Suppl. 2):21–40. doi: 10.1111/bdi.12342
7. Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. *Aust New Zealand J Psychiatry* (2009) 43:1105–17. doi: 10.3109/00048670903279887
8. Bora E, Harrison BJ, Yucel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol Med.* (2013) 43:2017–26. doi: 10.1017/S0033291712002085
9. Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology* (2015) 40:2025–37. doi: 10.1038/npp.2015.52
10. Watson S, Gallagher P, Porter RJ, Smith MS, Herron LJ, Bulmer SG, et al. A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. *Biol Psychiatry* (2012) 72:943–9. doi: 10.1016/j.biopsych.2012.05.029
11. Porter RJ, Bowie CR, Jordan J, Malhi GS. Cognitive remediation as a treatment for major depression: a rationale, review of evidence and recommendations for future research. *Aust New Zealand J Psychiatry* (2013) 47:1165–75. doi: 10.1177/0004867413502090
12. Alexopoulos GS, Raue PJ, Kiosses DN, Mackin RS, Kanellopoulos D, McCulloch C, et al. Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction: effect on disability. *Arch Gen Psychiatry* (2011) 68:33–41. doi: 10.1001/archgenpsychiatry.2010.177
13. Dunkin JJ, Leuchter AF, Cook IA, Kasl-Godley JE, Abrams M, Rosenberg-Thompson S. Executive dysfunction predicts nonresponse to fluoxetine in major depression. *J Affect Disord.* (2000) 60:13–23. doi: 10.1016/S0165-0327(99)00157-3
14. Taylor BP, Bruder GE, Stewart JW, McGrath PJ, Halperin J, Ehrlichman H, et al. Psychomotor slowing as a predictor of fluoxetine nonresponse in depressed outpatients. *Am J Psychiatry* (2006) 163:73–8. doi: 10.1176/appi.ajp.163.1.73
15. Herrera-Guzman I, Gudayol-Ferre E, Lira-Mandujano J, Herrera-Abarca J, Herrera-Guzman D, Montoya-Perez K, et al. Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. *Psych Res.* (2008) 160:72–82. doi: 10.1016/j.psychres.2007.04.012
16. Gudayol-Ferre E, Herrera-Guzman I, Camarena B, Cortes-Penagos C, Herrera-Abarca JE, Martinez-Medina P, et al. The role of clinical variables, neuropsychological performance and SLC6A4 and COMT gene polymorphisms on the prediction of early response to fluoxetine in major depressive disorder. *J Affect Disord.* (2010) 127:343–51. doi: 10.1016/j.jad.2010.06.002
17. Gudayol-Ferre E, Herrera-Guzman I, Camarena B, Cortes-Penagos C, Herrera-Abarca JE, Martinez-Medina P, et al. Prediction of remission of depression with clinical variables, neuropsychological performance, and serotonergic/dopaminergic gene polymorphisms. *Hum Psychopharmacol.* (2012) 27:577–86. doi: 10.1002/hup.2267
18. Gudayol-Ferre E, Guardia-Olmos J, Pero-Cebollero M, Herrera-Guzman I, Camarena B, Cortes-Penagos C, et al. Prediction of the time-course pattern of remission in depression by using clinical, neuropsychological, and genetic variables. *J Affect Disord.* (2013) 150:1082–90. doi: 10.1016/j.jad.2013.04.024
19. Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. *Int J Neuropsychopharmacol.* (2014) 17:1805–13. doi: 10.1017/S1461145714001011
20. Etkin A, Patenaude B, Song YJ, Usherwood T, Rekshan W, Schatzberg AF, et al. A cognitive-emotional biomarker for predicting remission with antidepressant medications: a report from the iSPOT-D trial. *Neuropsychopharmacology* (2015) 40:1332–42. doi: 10.1038/npp.2014.333
21. Mikoteit T, Hemmeter U, Eckert A, Brand S, Bischof R, Delini-Stula A, et al. Improved alertness is associated with early increase in serum brain-derived neurotrophic factor and antidepressant treatment outcome in major depression. *Neuropsychobiology* (2015) 72:16–28. doi: 10.1159/000437439
22. Murrough JW, Wan LB, Iacoviello B, Collins KA, Solon C, Glicksberg B, et al. Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response. *Psychopharmacology* (2014). 231:481–8. doi: 10.1007/s00213-013-3255-x
23. Murrough JW, Burdick KE, Levitch CF, Perez AM, Brallier JW, Chang LC, et al. Neurocognitive effects of ketamine and association with antidepressant response in individuals with treatment-resistant depression: a randomized controlled trial. *Neuropsychopharmacology* (2015) 40:1084–90. doi: 10.1038/npp.2014.298
24. Clery-Melin ML, Gorwood P. A simple attention test in the acute phase of a major depressive episode is predictive of later functional remission. *Depress Anxiety* (2017) 34:159–70. doi: 10.1002/da.22575
25. Bastos AG, Guimarães LS, Trentini CM. Predictors of response in the treatment of moderate depression. *Revista Brasileira de Psiquiatria* (2017) 39:12–20. doi: 10.1590/1516-4446-2016-1976
26. Kalayam B, Alexopoulos GS. A preliminary study of left frontal region error negativity and symptom improvement in geriatric depression. *Am J Psychiatry* (2003) 160:2054–6. doi: 10.1176/appi.ajp.160.11.2054
27. Doraiswamy PM, Krishnan KR, Oxman T, Jenkyn LR, Coffey DJ, Burt T, et al. Does antidepressant therapy improve cognition in elderly depressed patients? *J Gerontol Ser A* (2003) 58:1137–44. doi: 10.1093/gerona/58.12.M1137
28. Alexopoulos GS, Kiosses DN, Murphy C, Heo M. Executive dysfunction, heart disease burden, and remission of geriatric depression. *Neuropsychopharmacology* (2004) 29:2278–84. doi: 10.1038/sj.npp.1300557
29. Alexopoulos GS, Kiosses DN, Heo M, Murphy CF, Shanmugham B, Gunning-Dixon F. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry* (2005) 58:204–10. doi: 10.1016/j.biopsych.2005.04.024
30. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Kalayam B, Katz R, Kanellopoulos D, et al. Event-related potentials in an emotional go/no-go task and remission of geriatric depression. *Neuroreport* (2007) 18:217–21. doi: 10.1097/WNR.0b013e328013ceda
31. Murphy CF, Alexopoulos GS. Attention network dysfunction and treatment response of geriatric depression. *J Clin Exp Neuropsychol.* (2006) 28:96–100. doi: 10.1080/13803390490918101
32. Sneed JR, Roose SP, Keilp JG, Krishnan KR, Alexopoulos GS, Sackeim HA. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry* (2007) 15:553–63. doi: 10.1097/JGP.0b013e3180302513
33. Sneed JR, Keilp JG, Brickman AM, Roose SP. The specificity of neuropsychological impairment in predicting antidepressant non-response in the very old depressed. *Int J Geriatr Psychiatry* (2008) 23:319–23. doi: 10.1002/gps.1889
34. Morimoto SS, Gunning FM, Murphy CF, Kanellopoulos D, Kelly RE, Alexopoulos GS. Executive function and short-term remission of geriatric depression: the role of semantic strategy. *Am J Geriatr Psychiatry* (2011) 19:115–22. doi: 10.1097/JGP.0b013e3181e751c4
35. Alexopoulos GS, Manning K, Kanellopoulos D, McGovern A, Seirup JK, Banerjee S, et al. Cognitive control, reward-related decision making and outcomes of late-life depression treated with an antidepressant. *Psychol Med.* (2015) 45:3111–20. doi: 10.1017/S0033291715001075
36. de Groot MH, Nolen WA, Huijsman AM, Bouvy PF. Lateralized neuropsychological functioning in depressive patients before and after drug therapy. *Biol Psychiatry* (1996) 40:1282–7. doi: 10.1016/0006-3223(95)00654-0
37. Majer M, Ising M, Kunzel H, Binder EB, Holsboer F, Modell S, et al. Impaired divided attention predicts delayed response and risk to relapse in subjects with depressive disorders. *Psychol Med.* (2004) 34:1453–63. doi: 10.1017/S0033291704002697
38. Gallagher P, Robinson LJ, Gray JM, Porter RJ, Young AH. Neurocognitive function following remission in major depressive disorder: potential objective marker of response? *Aust New Zealand J Psychiatry* (2007) 41:54–61. doi: 10.1080/00048670601057734
39. Gorlyn M, Keilp JG, Grunebaum MF, Taylor BP, Oquendo MA, Bruder GE, et al. Neuropsychological characteristics as predictors of SSRI treatment response in depressed subjects. *J Neural Transmiss.* (2008) 115:1213–9. doi: 10.1007/s00702-008-0084-x
40. Withall A, Harris LM, Cumming SR. The relationship between cognitive function and clinical and functional outcomes in major depressive disorder. *Psychol. Med.* (2009) 39:393–402. doi: 10.1017/S0033291708003620

41. Spronk D, Arns M, Barnett KJ, Cooper NJ, Gordon E. An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: a pilot study. *J Affect Disord.* (2011) 128:41–8. doi: 10.1016/j.jad.2010.06.021
42. Talarowska M, Zboralski K, Galecki P. Correlations between working memory effectiveness and depression levels after pharmacological therapy. *Psychiatria Polska* (2013) 47:255–67.
43. Bruder GE, Alvarenga JE, Alschuler D, Abraham K, Keilp JG, Hellerstein DJ, et al. Neurocognitive predictors of antidepressant clinical response. *J Affect Disord.* (2014) 166:108–14. doi: 10.1016/j.jad.2014.04.057
44. Lin K, Xu G, Lu W, Ouyang H, Dang Y, Lorenzo-Seva U, et al. Neuropsychological performance in melancholic, atypical and undifferentiated major depression during depressed and remitted states: a prospective longitudinal study. *J Affect Disord.* (2014) 168:184–91. doi: 10.1016/j.jad.2014.06.032
45. Crane NA, Jenkins LM, Bhaumik R, Dion C, Gowins JR, Mickey BJ, et al. Multidimensional prediction of treatment response to antidepressants with cognitive control and functional MRI. *Brain* (2017) 140:472–86. doi: 10.1093/brain/aww326
46. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Arch General Psychiatry* (1999) 56:713–8. doi: 10.1001/archpsyc.56.8.713
47. Potter GG, Kittinger JD, Wagner HR, Steffens DC, Krishnan KR. Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacology* (2004) 29:2266–71. doi: 10.1038/sj.npp.1300551
48. Story TJ, Potter GG, Attix DK, Welsh-Bohmer KA, Steffens DC. Neurocognitive correlates of response to treatment in late-life depression. *Am J Geriatr Psychiatry* (2008) 16:752–9. doi: 10.1097/JGP.0b013e31817e739a
49. Bingham KS, Whyte EM, Meyers BS, Mulsant BH, Rothschild AJ, Banerjee S, et al. Relationship between cerebrovascular risk, cognition, and treatment outcome in late-life psychotic depression. *Am J Geriatr Psychiatry* (2015) 23:1270–5. doi: 10.1016/j.jagp.2015.08.002
50. Kundermann B, Hemmeter-Spernal J, Strate P, Gebhardt S, Huber M, Krieg JC, et al. Neuropsychological predictors of the clinical response to cognitive-behavioral therapy in patients with major depression. *Zeitschrift Neuropsychol.* (2015) 26:87–98. doi: 10.1024/1016-264X/a000130
51. Martin DM, Yeung K, Loo CK. Pre-treatment letter fluency performance predicts antidepressant response to transcranial direct current stimulation. *J Affect Disord.* (2016) 203:130–5. doi: 10.1016/j.jad.2016.05.072
52. McInerney SJ, McNeely HE, Geraci J, Giacobbe P, Rizvi SJ, Ceniti AK, et al. Neurocognitive predictors of response in treatment resistant depression to subcallosal *Cingulate gyrus* deep brain stimulation. *Front Hum Neurosci* (2017) 11:74. doi: 10.3389/fnhum.2017.00074
53. Beaudreau SA, Rideaux T, O'Hara R, Arean P. Does cognition predict treatment response and remission in psychotherapy for late-life depression? *Am J Geriatr Psychiatry* (2015) 23:215–9. doi: 10.1016/j.jagp.2014.09.003
54. Morimoto SS, Gunning FM, Wexler BE, Hu W, Ilieva I, Liu J, et al. Executive dysfunction predicts treatment response to neuroplasticity-based computerized cognitive remediation (nCCR-GD) in elderly patients with major depression. *Am J Geriatr Psychiatry* (2016) 24:816–20. doi: 10.1016/j.jagp.2016.06.010
55. Marcos T, Portella MJ, Navarro V, Gasto C, Rami L, Lazaro L, et al. Neuropsychological prediction of recovery in late-onset major depression. *Int J Geriatr Psychiatry* (2005) 20:790–5. doi: 10.1002/gps.1363
56. Saveanu R, Etkin A, Duchemin AM, Goldstein-Piekarski A, Gyurak A, Debattista C, et al. The international Study to Predict Optimized Treatment in Depression (iSPOT-D): outcomes from the acute phase of antidepressant treatment. *J Psychiatr Res.* (2015) 61:1–12. doi: 10.1016/j.jpsychires.2014.12.018
57. Blier P, Saint-Andre E, Hebert C, de Montigny C, Lavoie N, Debonnel G. Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. *Int J Neuropsychopharmacol.* (2007) 10:41–50. doi: 10.1017/S1461145705006395
58. Debonnel G, Saint-Andre E, Hebert C, de Montigny C, Lavoie N, Blier P. Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *Int J Neuropsychopharmacol.* (2007) 10:51–61. doi: 10.1017/S1461145705006413
59. Owens MJ, MorganWN, Plott SJ, Nemeroff CB. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Therapeut.* (1997). 283:1305–22.
60. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* (2009) 373:746–58. doi: 10.1016/S0140-6736(09)60046-5
61. Parker G. Classifying depression: should paradigms lost be regained? *Am J Psychiatry* (2000) 157:1195–203. doi: 10.1176/appi.ajp.157.8.1195
62. Parker G, Blanch B, Paterson A, Hadzi-Pavlovic D, Sheppard E, Manicavasagar V, et al. The superiority of antidepressant medication to cognitive behavior therapy in melancholic depressed patients: a 12-week single-blind randomized study. *Acta Psychiatr Scandanavica* (2013) 128:271–81. doi: 10.1111/acps.12049
63. Parker G, Bassett D, Outhred T, Morris G, Hamilton A, Das P, et al. Defining melancholia: a core mood disorder. *Bipolar Disord.* (2017) 19:235–7. doi: 10.1111/bdi.12501
64. Cropley VL, Fujita M, Innis RB, Nathan PJ. Molecular imaging of the dopaminergic system and its association with human cognitive function. *Biol. Psychiatry* (2006) 59:898–907. doi: 10.1016/j.biopsych.2006.03.004
65. Murrough JW, Collins KA, Fields J, DeWilde KE, Phillips ML, Mathew SJ, et al. Regulation of neural responses to emotion perception by ketamine in individuals with treatment-resistant major depressive disorder. *Transl Psychiatry* (2015b) 5:e509. doi: 10.1038/tp.2015.10
66. Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL, et al. Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry* (2000) 48:627–40. doi: 10.1016/S0006-3223(00)00976-8
67. Bearden CE, Glahn DC, Monkul ES, Barrett J, Najt P, Villarreal V, et al. Patterns of memory impairment in bipolar disorder and unipolar major depression. *Psychiatry Res.* (2006) 142:139–50. doi: 10.1016/j.psychres.2005.08.010
68. Kessing LV. Cognitive impairment in the euthymic phase of affective disorder. *Psychol Med.* (1998) 28:1027–38. doi: 10.1017/S0033291798006862
69. Gorwood P, Corruble E, Falissard B, Goodwin GM. Toxic effects of depression on brain function: impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *Am J Psychiatry* (2008) 165:731–9. doi: 10.1176/appi.ajp.2008.07040574
70. Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. *Biol Psychiatry* (2002) 52:543–58. doi: 10.1016/S0006-3223(02)01468-3
71. Thomas AJ, Gallagher P, Robinson LJ, Porter RJ, Young AH, Ferrier IN, et al. A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychol Med.* (2009) 39:725–33. doi: 10.1017/S0033291708004042
72. Miskowiak KW, Burdick KE, Martinez-Aran A, Bonnin CM, Bowie CR, Carvalho AF, et al. Methodological recommendations for cognition trials in bipolar disorder by the International Society for bipolar disorders targeting cognition task force. *Bipolar Disord.* (2017) 19:614–26. doi: 10.1111/bdi.12534
73. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annu Rev Psychol.* (2002) 53:545–74. doi: 10.1146/annurev.psych.53.100901.135148
74. Siegle GJ, Ghinassi F, Thase ME. Neurobehavioral therapies in the 21st century: summary of an emerging field and an extended example of cognitive control training for depression. *Cogn Ther Res.* (2007) 31:235–62. doi: 10.1007/s10608-006-9118-6
75. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. *Annu Rev Clin Psychol.* (2010) 6:285–312. doi: 10.1146/annurev.clinpsy.121208.131305
76. Roiser JP, Elliott R, Sahakian BJ. Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology* (2012) 37:117–36. doi: 10.1038/npp.2011.183
77. Khan A, Leventhal RM, Khan SR, Brown WA. Severity of depression and response to antidepressants and placebo: an analysis of the Food and

Drug Administration database. *J Clin Psychopharmacol.* (2002) 22:40–5. doi: 10.1097/00004714-200202000-00007

78. Douglas KM, Gallagher P, Robinson LJ, Carter JD, McIntosh VV, Frampton CM, et al. Prevalence of cognitive impairment in major depression and bipolar disorder. *Bipolar Disord.* (2018). doi: 10.1111/bdi.12602
79. Shilyansky C, Williams LM, Gyurak A, Harris A, Usherwood T, Etkin A. Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *Lancet Psychiatry* (2016) 3:425–35. doi: 10.1016/S2215-0366(16)00012-2
80. Pimontel MA, Rindskopf D, Rutherford BR, Brown PJ, Roose SP, Sneed JR. A meta-analysis of executive dysfunction and antidepressant treatment response in late-life depression. *Am J Geriatr Psychiatry* (2016) 24:31–41. doi: 10.1016/j.jagp.2015.05.010
81. Bourke C, Porter RJ, Carter JD, McIntosh VV, Jordan J, Bell C, et al. Comparison of neuropsychological functioning and emotional processing in major depression and social anxiety disorder subjects, and matched healthy controls. *Australian New Zealand J Psychiatry* (2012) 46:972–81. doi: 10.1177/00048674124 51502
82. Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *Am J Psychiatry* (2003) 160:990–2. doi: 10.1176/appi.ajp.160.5.990

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RS and handling Editor declared their shared affiliation at the time of the review.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 03 September 2018
doi: 10.3389/fpsyt.2018.00396

Haste or Speed? Alterations in the Impact of Incentive Cues on Task Performance in Remitted and Depressed Patients With Bipolar Disorder

Henry W. Chase[1]*, *Jay C. Fournier*[1], *Haris Aslam*[1], *Richelle Stiffler*[1], *Jorge R. Almeida*[2], *Barbara J. Sahakian*[3] and *Mary L. Phillips*[1]

[1] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [2] Department of Psychiatry, Dell Medical School, University of Texas at Austin, Austin, TX, United States, [3] Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

OPEN ACCESS

Edited by:
Catherine Harmer,
Warneford Hospital, United Kingdom

Reviewed by:
Mirko Manchia,
Università Degli Studi di Cagliari, Italy
Peter Gallagher,
Newcastle University, United Kingdom

***Correspondence:**
Henry W. Chase
chaseh@upmc.edu

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: 30 April 2018
Accepted: 07 August 2018
Published: 03 September 2018

Citation:
Chase HW, Fournier JC, Aslam H, Stiffler R, Almeida JR, Sahakian BJ and Phillips ML (2018) Haste or Speed? Alterations in the Impact of Incentive Cues on Task Performance in Remitted and Depressed Patients With Bipolar Disorder. Front. Psychiatry 9:396. doi: 10.3389/fpsyt.2018.00396

A variety of evidence suggests that bipolar disorder is associated with disruptions of reward related processes, although the properties, and scope of these changes are not well understood. In the present study, we aimed to address this question by examining performance of patients with bipolar disorder (30 depressed bipolar; 35 euthymic bipolar) on a motivated choice reaction time task. We compared performance with a group of healthy control individuals ($n = 44$) and a group of patients with unipolar depression ($n = 41$), who were matched on several demographic variables. The task consists of an "odd-one-out" discrimination, in the presence of a cue signaling the probability of reward on a given trial (10, 50, or 90%) given a sufficiently fast response. All groups showed similar reaction time (RT) performance, and similar shortening of RT following the presentation of a reward predictive cue. However, compared to healthy individuals, the euthymic bipolar group showed a relative increase in commission errors during the high reward compared to low condition. Further correlational analysis revealed that in the healthy control and unipolar depression groups, participants tended either to shorten RTs for the high rather than low reward cue a relatively large amount with an increase in error rate, or to shorten RTs to a lesser extent but without increasing errors to the same degree. By contrast, reward-related speeding and reward-related increase in errors were less well coupled in the bipolar groups, significantly so in the BPD group. These findings suggest that although RT performance on the present task is relatively well matched, there may be a specific failure of individuals with bipolar disorder to calibrate RT speed and accuracy in a strategic way in the presence of reward-related stimuli.

Keywords: bipolar disorder, reinforcement (psychology), reaction time, motivation, major depressive disorder

INTRODUCTION

Bipolar disorder (BD) is characterized by modified behavioral and neural responsiveness to reward (1–3). Although individuals with BD report a heightened desire to attain happiness (4), patients' lives are typically characterized by instability and low levels of (eudaimonic) well-being (5). One potential explanation for this discrepancy is that there is an imbalance in the neural systems controlling the pursuit of reward. Responsiveness to reward in BD may better reflect the arousing or activating properties of reinforcement-related stimuli rather than enhanced hedonic responses (6), akin to a non-specific invigoration of behavior elicited by reward-related stimuli (7). In general, invigoration is likely to be adaptive in a reward-rich environment, but there may also be deleterious consequences [e.g., (8)] which may be relevant for BD.

Alterations in the performance of BD on reinforcement learning paradigms have been reported (9, 10), as well as altered decision making (11), but these studies vary in their emphasis on risk taking, blunted reward sensitivity and cognitive flexibility. In the present study, we employed the Cued Reinforcement Reaction Time (CRRT) task, a motivated reaction time task which has been employed in studies of 5-HT (serotonin) manipulations (12) and patients (13, 14). The reinforcement contingencies on the task should prompt the participant to shorten their reaction times on high reinforcement trials compared to the low trials, so primarily the task is used as an index of the motivational impact of cues on a simple cognitive task. In a previous investigation with the CRRT (12), manipulation of central nervous system 5-HT using acute tryptophan depletion (ATD) reduced reinforcement related speeding in a group of healthy individuals. In addition, the pattern of errors changed, with a relative reduction of errors in the high reinforcement condition.

With regard to BD, we considered two hypotheses. First, there may be generally inflated urgency across all rewarding contexts, or a preference for speed over accuracy. Second, there may be an impairment in the contextual calibration of urgency. It is often assumed that increasing impulsivity is broadly maladaptive [e.g., (15)]. However, there is also a concept of "functional" impulsivity (16), in which rapid if inaccurate decisions are necessary in order to obtain reward and are thereby adaptive. Thus, impaired calibration could lead to hasty and inaccurate decision making in reward-sparse environments when accuracy is needed, but also excessively conservative decision making in reward-rich environments. We performed a detailed analysis of task performance to investigate these possibilities.

We recruited four groups of participants (bipolar euthymic, bipolar depressed, major depressive disorder (MDD), and healthy controls), and hypothesized that the normal pattern of reward-related speeding would be altered in individuals with bipolar disorder. Note that these predictions are focused on the notion that BD patients (euthymic or depressed) would show altered impulsivity that would be detected on the CRRT paradigm. This design allows the impact of mood state to be largely differentiated from a BD-related trait abnormality. In a previous study with unipolar depressed patients (14), we observed an overall intact pattern of responding on the paradigm (i.e., similar reward-related speeding to controls), and even enhanced performance on some metrics. We also sought to determine whether a similar finding could be identified in the present data set. Our analytical strategy incorporated conventional reaction time (RT) and error difference scores. To provide further support to our conclusions, we supplemented this analysis with a simple reinforcement learning-based approach, instantiated within a general linear model (GLM).

METHODS

Participants

Thirty currently depressed adults with bipolar disorder (BPD) type I, 35 currently Euthymic individuals with bipolar disorder (BPE) type I, and 41 currently depressed adults with MDD participated in the study. All BPE/BPD/MDD participants were diagnosed according to DSM-IV criteria using the Structured Clinical Interview for DSM-IV-Research-Version [SCID-P: (17)]. All BPD and MDD participants were in a Major Depressive Episode, as determined by SCID-P criteria, at the time of a functional magnetic resonance imaging (fMRI) scan which occurred ∼1 week prior to the behavioral testing session at which the present data was collected. Data obtained from this scanning session have been previously reported (6, 18–20). Current mood state was confirmed by having a Hamilton Rating Scale for Depression (HRSD-25) $\geq$17 (21) and a Young Mania Rating Scale [YMRS: (22)] score $\leq$10 on the day of the test (unless it occurred <4 days after the scanning session), although three BPD and five MDD individuals meeting SCID-P criteria for depressive episode had a HRSD-25 score between 11 and 17 on the test day, while three BPE had scores of 17 or over. All participants also completed the Spielberger State Anxiety Inventory on the test day (23). Prevalence of lifetime comorbid anxiety and substance use disorders are reported in **Table 1**. Importantly, all BPE/BPD/MDD participants were free from alcohol/substance abuse or dependence for a minimum of 3 months prior to the study (range: 4–235 months). Forty-four healthy adult control participants (HC) with no previous personal or family history of psychiatric illness in first-degree relatives participated in the study. All HC participants were also free of previous or current alcohol/illicit substance abuse. All participants were right-handed and native English speaking. The study protocol was approved by the University of Pittsburgh Institutional Review Board. After complete description of the study to the participants, written informed consent was obtained.

Further exclusion criteria for all participants included history of head injury, systemic medical illness, cognitive impairment, premorbid IQ estimate <85 (as derived from the National Adult Reading Test: NART), schizophrenia/schizo-affective disorder and rapid cycling disorder. All included participants showed <21 errors per condition/block, and <8 time-outs. The final participant numbers per group listed above and in **Table 1** do not include a further three individuals with BPE and two with MDD who were excluded due to poor task performance (>9 time outs). A high number of timeouts might have been reflective

TABLE 1 | Demographic and clinical information for participants in the four groups.

	Healthy controls	Major depressive disorder	Bipolar depression	Bipolar euthymic	Group differences
Gender (M:F)	15:29	9:32	6:24	12:23	$X^2 = 3.19$, $p = 0.36$
Age (years; mean/S.D.)	33.60 (6.093)	32.29 (7.74)	32.15 (8.85)	32.62 (8.08)	$F_{(3, 146)} < 1$
NART IQ (mean/S.D.)	112.32 (9.53)	112.32 (9.53)	110.22 (10.047)	112.97 (9.30)	$F_{(3, 146)} < 1$
Years of Education (mean/S.D.)	6.41 (1.28)	6.10 (1.28)	5.30 (1.12)	6.31 (1.21)	$F_{(3, 146)} = 5.47$, $p = 0.001$ (BPD<all other groups)
HRSD 25 (mean/S.D.)	1.75 (1.97)	25.90 (6.14)	25.90 (6.099)	7.43 (6.87)	$F_{(3, 146)} = 202.34$, $p < 0.001$
Illness Duration (mean/S.D.)	N/A	13.95 (7.66)	16.41 (8.18)	13.074 (7.60)	$F_{(2, 103)} = 1.57$, $p = 0.21$
Number of Manic Episodes	N/A	N/A	1.80 (0.96)	2.23 (1.46)	$F_{(1, 63)} = 1.89$, $p = 0.17$
Number of Depressive Episodes	N/A	2.93 (1.37)	3.03 (1.33)	2.31 (1.66)	$F_{(2, 103)} = 2.84$, $p = 0.063$
YMRS (mean/S.D.)	0.41 (0.84)	3.17 (2.50)	4.33 (2.31)	2.31 (2.58)	$F_{(3, 146)} = 24.71$, $p < 0.001$
State Anxiety (mean/S.D.)	27.25 (7.85)	55.63 (10.087)	53.80 (11.31)	33.97 (10.92)	$F_{(3, 146)} = 79.29$, $p < 0.001$
Lifetime Comorbid Anxiety Disorders (W:WO)	0:44	30:11	22:8	11:24	
Lifetime Substance Use Disorders (W:WO)	0:44	15:26	12:18	14:21	
Psychotropic Medication Load (mean/S.D.)	0 (0)	2.44 (2.062)	3.53 (2.30)	3.09 (1.72)	$F_{(3, 146)} = 33.77$, $p < 0.001$ (HC<all patient groups, otherwise no significant differences)
Antipsychotic (T:NT)	0:44	3:38	19:11	22:13	
Antidepressant (T:NT) (includes Buproprion)	0:44	30:11	12:18	12:23	
Mood Stabilizer (T:NT)	0:44	6:35	16:14	23:12	
Anxiolytic (predominantly Benzodiazepine) (T:NT)	0:44	10:31	8:22	4:31	

T:NT, taking: not taking; W:WO, with:without symptom.

of a failure to understand the instructions fully, and would have resulted in a reduction in the number of trials in which performance feedback was provided. Timeouts also reduce the amount of data available for modeling within the GLM. Two further participants (one BPE and one HC) were excluded on the basis of a relatively poor GLM fit (log likelihood<1100/Z score of the residual variance relative to overall mean Z>7; all included participants log likelihood = 1150–1350), which was generally reflective of abnormal performance (outliers) on one or more metric.

Procedure

The paradigm was the same as that employed by Cools et al. (12). Participants performed two short practice blocks (20 trials) of a task, based on the circles task of Duncan et al. (24), in which they had to select the odd-one-out of three stimuli, within 2,000 ms. The mean and standard deviation of the participant's reaction time on the second practice block were recorded, and used as the "reward threshold" for the next stage of the task. Participants then performed two longer blocks (96 trials each) of a similar task, which contained a reinforcement component via the potential to win points. Points rewards were available on some trials, and were dependent on subjects' accuracy and speed, as well as the presence of rectangular cues which surrounded the area where the circles were presented, and were presented before the circles were presented. One cue predicted reward availability on 90% of trials (high probability cue), the second on 50% (medium probability cue), and the third on 10% of trials (low probability cue). Colors used for these cues were always red, blue and yellow, and subjects were randomly assigned to one of two mappings between cue and reward probability. Of the 96 trials in each block, 32 trials were performed with each cue type. There were 12 different arrays of three circles, and these were counterbalanced within cues such that there were no cue repetitions, and only two response repetitions occurred. If rewards were available on a given trial and the subject responded both correctly and faster than their reward threshold, the subject would receive 100 points, a green smiling face and a flourish sound. If the same were true, but the subject had responded slower than their reward threshold, they would receive 1 point, a green smiling face and a high frequency tone. Finally, if the subject was incorrect on trials where reward was available, they would receive negative feedback (a red frowning face and a low frequency tone, but no loss of points). If reward was not available on a given trial, no feedback was provided.

Data Analysis: Basic Analyses

First, raw RT data were transformed using a reciprocal transform [see (25)]. For basic analyses, mean reciprocal RTs from correct trials were calculated for each cue (high/medium/low) and block

(first/second) separately. Repeated-measures ANOVA was then conducted for the resulting variables, including effects of block and cue as a within-participant factors, and the effect of group as a between-participant factor. Following previous studies (26), we also computed a measure of RT speeding, contrasting the high vs. low reward probability cue following Z transformation of the raw RT values (with reference to the mean and standard deviation for all cues within a block). We focused on block 2 only, as the reward contingencies were more likely to have been learned by that stage. All parametric analyses were confirmed by including years of education, age and gender as covariates. In all cases, findings were similar and these analyses are not reported. Following the suggestion of a reviewer, we also performed an additional analysis involving number of manic episodes in the bipolar groups alone (BPE/BPD).

Due to their non-normal distribution, error scores (per block/cue) were analyzed using non-parametric tests (Kruskal–Wallis test). Similar difference scores reflecting the effect of high vs. low probability cues for block 2 were calculated to compare with RT speeding metrics described above. Speed/accuracy relationships were investigated in two ways: first, with a simple Spearman's Rho correlation; second, using ordinal logistic regression. For the latter analysis, six error categories (−3 to +2 errors for high vs. low cue trials, block 2) containing roughly similar numbers of individuals were created to reduce model complexity.

Data Analysis: General Linear Model

As a follow up analysis, reciprocal RTs from the whole task (both blocks) were fit within a single general linear model [GLM: (25, 27)] separately for each participant. The goal of this modeling was broadly to demonstrate that the data are consistent with a Reinforcement Learning (RL) model, and that similar findings could be obtained using different modeling approaches. Our initial analyses suggested that the data did not provide strong constraints over multiple possible free parameters—specifically, the design did not allow unique identification of these parameters. We therefore set them either on the basis of prior work or to reflect a nominal magnitude ranking. These arbitrary decisions were justified insofar as they were unlikely to have a substantial impact on the overall pattern of data—at least with respect to group differences. To correct for autocorrelated properties of the timeseries, an AR(3) ARIMA model [see (25)] was fit using MATLAB (regARIMA function), and fixed effects at the subject level were thereby obtained. The model contained the following components as independent (predictor) variables: the first 5 trials per block [see (25)]; error trials; post error trials; a linear trend to correct for non-specific improvement on the task (trial number); and reward expectancy generated from a reinforcement learning model. The latter component was most relevant to our focus, and was derived from the following equation:

$$\mathrm{Q(cue,t)} \leftarrow \mathrm{Q(cue,t)} + \mathrm{alpha}*(\mathrm{outcome(t)} - \mathrm{Q(cue,t)})$$

The learning rate (alpha) was set to 0.2 for win or no-win outcomes [see (28)], but for punishment trials (signaled errors) it was set to 0.3 to reflect an increased salience of this condition. For 100 point wins, the outcome value was set to 3, and for 1 point wins it was set to 1. Trials on which responses were too slow were excluded from the analysis. We focused on the beta parameters associated with the Q-value regressor for further analysis, examining whether there were group differences using a combination of one-way ANOVA and a Bayesian test of the null hypothesis (29), and also recapitulated the ordinal logistic regression analysis described above using the *Q*-value beta value instead of the RT speeding measure.

Effect of Medication

We computed: (1) medication load, an index that reflects the number and dose of different medications, as in our previous neuroimaging studies on bipolar disorder [e.g., (30) and 2] identified medication status (taking vs. not taking each of five main psychotropic medication subclasses: mood stabilizers/antipsychotics/antidepressant/anxiolytics/dopaminergic-antidepressants, e.g., Bupropion: see **Table 1**). Medication load calculation was based on a binary categorization of low and high dose groupings of antidepressants and mood stabilizers; a binary categorization of antipsychotics relative to mean effective daily dose of chlorpromazine hydrochloride; and a binary categorization of benzodiazepine dose relative to the recommended daily dose of each type of benzodiazepines. If a participant was not taking a given class of the medication, they would receive a score of 0, a low dose would receive a score of 1 and a high dose would receive a score of 2. Scores for each class of medication were added together to produce the final medication load score. Details of the patients' medications are presented in **Supplementary Table 1**. We tested whether the speed/accuracy relationships with the bipolar groups described within the ordinal logistic regression model were significant when medication (both main effect and medication by RT speeding interaction) was concurrently modeled.

RESULTS

Demographic Variables

The four groups were well matched for age, gender, and NART-estimated IQ (see **Table 1**). The groups differed on years of education, due to the BPD group showing a lower number of years of education.

Reaction Times and Overall Performance

Analysis of variance (ANOVA) conducted on the reciprocal RTs revealed a significant main effect of block [$F_{(1,\ 146)} = 48.38$, $p < 0.001$], a significant main effect of cue [$F_{(2.00,291.22)} = 10.94$, $p < 0.001$] and a significant block by cue interaction [$F_{(1.99,290.98)} = 15.73$, $p < 0.001$]. The main effect of group was not significant [$F_{(3,\ 146)} < 1$], neither were any significant interaction effects involving group (p's > 0.26). The robust effect of cue and cue by block interaction supported the hypothesis that RTs are sensitive to task contingencies. The presence of learning was further supported by significant high vs. low reward (z-transformed) RT differences in all four groups on the second block (t's > 2.71, p's

< 0.011: see **Figure 1**). Raw RT and error scores are presented in **Table 2**.

In terms of the number of points won overall, a significant main effect of block was observed [$F_{(1, 146)} = 42.31$, $p < 0.001$] which reflected a general increase in points scored in block 2, but no main effect of group [$F_{(3, 146)} = 1.34$, $p = 0.26$]. A marginal block by group interaction was also observed [$F_{(3, 146)} = 2.68$, $p = 0.049$]. Games-Howell non-parametric *post hoc* tests on the changing score from block 1 to block 2 revealed that healthy controls showed a relatively smaller increase in the number of points across blocks, and this was significantly lower than the BPD group ($p = 0.014$). No other significant findings were observed.

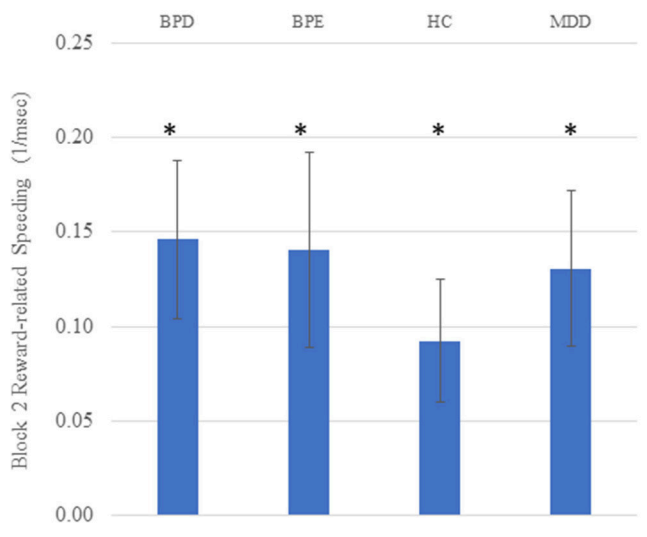

FIGURE 1 | Reward-related speeding (high vs. low reward cue) on the second block in all four groups. Higher scores on the Y axis indicate faster responding for high vs. low reward cues. Units are 1/ms; error bars reflect standard error of the mean; asterisks reflect the mean value being significantly greater than zero (*p*'s < 0.05).

Errors

Overall, all three groups showed similar rates of overall commission errors (χ^2 <1.2, *p*'s > 0.7 across both blocks and overall). Similar findings were seen with overall omission ("too late") errors (*p*'s > 0.45). Following the RT analysis by focusing on relative errors for the high vs. low reward cue in the second block, Kruskal–Wallis tests revealed a main effect of group ($\chi^2 = 9.26$, df = 3, $p = 0.026$). The only *post-hoc* test reaching significance when corrected for the number of possible group ($n = 6$) comparisons was the difference between control and BPE individuals ($Z = 2.76$, $p = 0.006$), with BPE individuals making relatively more errors in the high reward than the low reward condition than the controls in the second block (see **Figure 2**). The BPE group also tended to make relatively more errors on high vs. low reward trials in the second block than the BPD group ($p = 0.027$) and the MDD group ($p = 0.090$). Looking at differential error rates within the groups, the BPE group was the only group to show a significant difference between the block 2 stimuli in terms of error rates, showing significantly higher error rates to the high compared to low reward stimuli ($Z = 2.49$, $p = 0.013$). The three other groups showed similar error rates on block 2 across stimuli. Finally, a difference between the groups on high vs. low error rate was not seen on the first block ($\chi^2 = 3.77$, df = 3, $p = 0.29$). We also investigated the impact of the number of prior manic episodes on the reward-related error rate within the BPE/BPD groups. A significant relationship was observed ($\rho = -0.28$, $p = 0.027$, $n = 65$), with relatively greater errors on the high reward trials being observed in patients who had experienced greater numbers of manic episodes.

Relationship of Speed and Accuracy

As described above, the strongest metric of reward-related speeding was high vs. low reward RT difference on the second block. If participants are differentially balancing speed and accuracy, we might expect that, across individuals, shorter RTs in the high reward condition would come at the cost of a relatively increased error rate. Across all individuals, this hypothesis was supported ($\rho = 0.31$, $p < 0.001$), and strongly in the HC ($\rho =$

TABLE 2 | Raw RT (ms units) and error scores (mean/standard deviation) for each group, for each block (1 and 2), and cue (high, mid, and low reward probability).

	HC	MDD	BPD	BPE
Block 1 Low RT	657.71 (115.85)	691.84 (155.07)	718.12 (186.63)	670.25 (158.89)
Block 1 Mid RT	657.40 (116.46)	700.02 (166.11)	739.03 (191.60)	683.16 (161.79)
Block 1 High RT	651.36 (117.03)	682.39 (157.19)	730.93 (189.76)	686.52 (177.71)
Block 2 Low RT	635.94 (112.85)	669.91 (153.75)	676.12 (159.03)	665.56 (165.75)
Block 2 Mid RT	625.67 (114.62)	659.35 (151.70)	665.75 (163.11)	655.66 (170.53)
Block 2 High RT	630.10 (121.57)	653.30 (152.25)	657.13 (159.34)	644.11 (156.42)
Block 1 Low Error	3.23 (3.33)	2.44 (2.11)	2.27 (2.18)	3.03 (2.83)
Block 1 Mid Error	2.91 (3.58)	2.68 (2.29)	2.20 (1.74)	2.97 (3.42)
Block 1 High Error	2.59 (2.60)	2.54 (2.45)	2.40 (1.98)	3.60 (3.87)
Block 2 Low Error	2.57 (2.94)	2.27 (2.06)	2.10 (1.79)	2.60 (2.67)
Block 2 Mid Error	2.39 (2.96)	1.66 (1.71)	2.07 (1.91)	2.34 (2.53)
Block 2 High Error	2.41 (3.21)	2.49 (2.42)	2.20 (2.21)	3.46 (3.56)

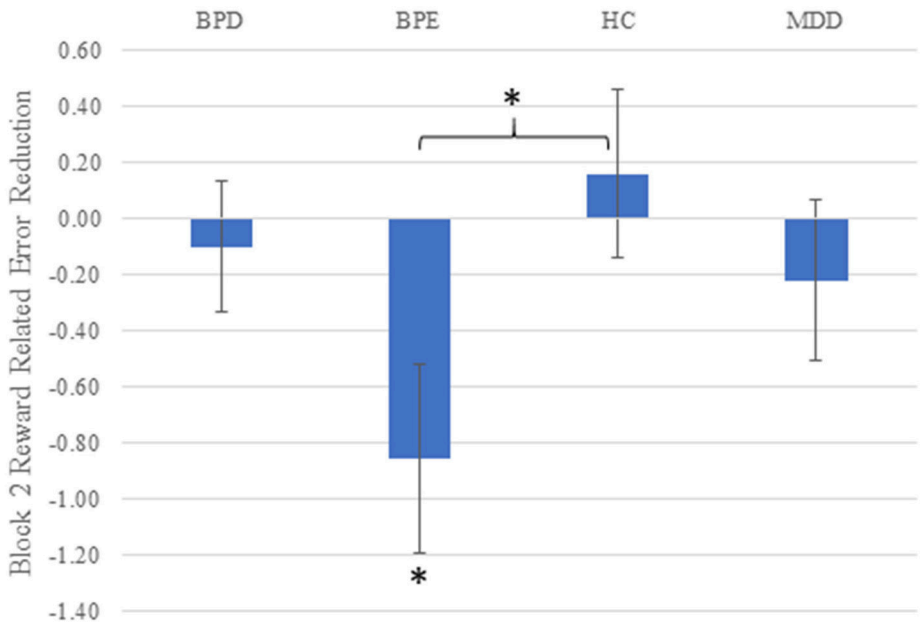

FIGURE 2 | Reward-related error rate (high vs. low reward cue) on the second block in all four groups. Higher scores on the Y axis indicate more accurate responding for high vs. low reward cues. Error bars reflect standard error of the mean; asterisks reflect the mean value being significantly greater than zero (BPE), or the BPE vs. control difference being significant (*p*'s < 0.05).

0.43, $p = 0.003$) and MDD ($\rho = 0.50$, $p = 0.001$) individually. In the BPE group, the relationship was significant if numerically smaller ($\rho = 0.37$, $p = 0.031$), and was not present in the BPD group ($\rho = -0.27$, $p = 0.15$: see **Figure 3**).

To model this finding more formally, we constructed an ordinal logistic regression model in which we aimed to predict the (high-low, block 2) errors from the amount of speeding differentially across the groups. The model confirmed a large main effect of high vs. low RT speeding (Wald = 13.00, $p < 0.001$). In addition, BPE showed main effect (Wald = 5.50, $p = 0.019$) (i.e., overall difference in high vs. low errors), but the BPE*RT speeding interaction term was not significant ($p = 0.35$). By contrast, the BPD group showed no significant main effect ($p = 0.29$) but significant interaction term (Wald = 9.089, $p = 0.003$).

General Linear Model

The Q value of the cue, as derived from the RL model, was related to RT as evidenced by a beta statistic that was significantly different from zero across all individuals [$t_{(149)} = 6.32$, $p < 0.001$]: trials where the cue value was higher had shorter RTs. Value-related RT speeding was correlated with block 2 high vs. low RT difference across all participants ($r = -0.49$, $p < 0.001$). No main effect of group was seen on this variable [$F_{(3, 146)} = 1.68$, $p = 0.17$]. Moreover, a Bayesian test of null hypothesis of currently depressed individuals (i.e., all MDD/BPD participants) vs. currently non-depressed individuals (all HC/BPE participants) revealed strong evidence for the null hypothesis of no difference between the groups (Bayes Factor = 12.91). Finally, of the three significant findings in the ordinal logistic regression model described in section Relationship of Speed and Accuracy, the main effect of value-related speeding (Wald = 4.91, $p = 0.027$), main effect of BPE (Wald = 3.41, $p = 0.065$) and BDE∗value-related speeding (Wald = 5.88, $p = 0.015$), all at least trended in the same direction as previously, while no further significant findings were observed.

Medication Effects

Including the presence of antipsychotic medications or mood stabilizers in the ordinal logistic regression model described in section General Linear Model reduced the effect of the BPE main effect ($p = 0.079$ or $p = 0.2$ respectively), while mood stabilizers themselves had a trend level effect ($p = 0.063$). A clearer influence was seen with overall medication load, which itself had a significant main effect (Wald = 4.23, $p = 0.040$) and load by speeding interaction (Wald = 4.58, $p = 0.032$). In this model, the BPE main effect was also reduced to marginal ($p = 0.058$). In all of these models, the significance of the BPD by speeding interaction was unaffected. Importantly, when the effect of antipsychotic medication, mood stabilizers, or medication load were examined in the BPE group alone, no significant differences in relative error rate were observed (all *p*'s>0.47). In other words, differential medication status within BPE participants was associated with similar patterns of reward-related error rates.

DISCUSSION

In the present study, we evaluated four groups of participants - euthymic and depressed patients with bipolar disorder, unipolar depressed individuals and healthy

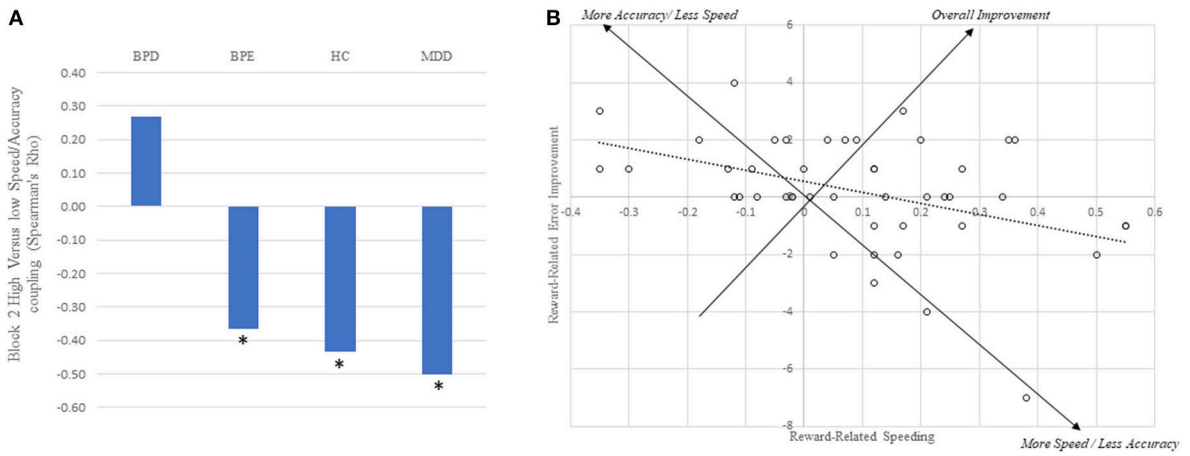

FIGURE 3 | Trade-off between increases in speed and accuracy for the high vs. low cue. **(A)** Between subject relationship between reward-related speed and accuracy improvements across all four groups. Asterisks reflect correlations being significantly different from zero (*p*'s < 0.05). **(B)** Plot of the individual subject data for the healthy control group alone, revealing the trade-off between speed and accuracy improvements. Note that a large proportion of individuals are in the upper right-hand quadrant, suggesting overall reward-related improvements.

controls—on a motivated reaction time paradigm. Across all individuals, significant, and similar RT speeding was observed across all four groups. An analysis using RT differences was confirmed with simple reinforcement learning (RL) model instantiated within a GLM. Second, different pattern of cue-related errors was observed in the BPE group: BPE individuals showed higher rates of errors in the high vs. low reward condition on block 2, whereas no other group showed this effect. Complementing this finding, greater numbers of manic episodes in the bipolar groups also predicted higher error rates in the high vs. low reward condition, suggesting that there may be dimensions of illness severity or chronicity which may generalize across the bipolar groups.

Accounting for differences in RT clarified the relative error rate finding further, as there were substantial individual differences in RT/errors. Controls and MDD groups showed strong negative relationships between high vs. low error difference scores, and high vs. low RT difference scores. This suggests that individuals adopt different strategies: on one end of the spectrum, they might reduce RTs dramatically for high reward cues at the cost of increased errors; at the other end, they might reduce RTs slightly and show relatively low error rates following the high reward cue. By contrast, both of the BD groups showed a complication of this predicted relationship: the BPE group showed an overall increase in errors in the high vs. low reward cue, while the BPD group showed a decoupling of high vs. low reward error rate and high vs. low RT.

Comparison With Previous Findings

Similar findings to the present were obtained by Mueller et al. (31): youth with pediatric bipolar disorder showed a higher error rate under the incentive condition of an anti-saccade task than healthy controls, while similar performance between the groups was seen on the no incentive condition, and on a pro-saccade task. This type of finding is compatible with our observations, insofar as the task incentives were associated with impaired performance in the bipolar group.

Existing data on the speed/accuracy trade off (SAT) in major depression are somewhat complex. Although MDD patients might be expected to favor accuracy over speed, Dillon et al. (32) demonstrated, using drift diffusion modeling of a flanker task, that a slower executive control process is offset by a slower prepotent bias. As a result, the SAT seen in MDD patients was roughly similar to that seen in controls. We were unable to replicate the finding of *enhanced* performance in MDD patients that we had previously reported (14). The present study cannot be considered an exact replication attempt, because the age of the participants was different between the samples (participants in the present sample were around ∼10 years younger), and different medications had been prescribed. Age may be a relevant dimension for further investigation because reanalysis of our previous findings suggested that age was positively related to overall errors and reaction time variability in the healthy control group (*r*'s = 0.44–0.50) but not in the patient group (*r*'s = −0.08: unpublished data). As the age range of the present sample is only partially overlapping with the previous sample, it is difficult to perform a direct replication of this finding here. Overall, a unifying conclusion of both datasets, which would be directly testable, is that MDD and/or antidepressant medications may prevent decline in overall RT performance in individuals >45 years old.

Nevertheless, the present findings strengthen an important conclusion of the previous study: namely, that reward-predictive cues can exert similar speeding effects on motivated behavior in depressed and healthy individuals. The present study was adequately powered to detect effects of similar magnitude to those reported in previous studies of psychopathology with this task [d = 0.77–1.29: (13, 14)]. These findings contribute to a growing literature describing areas of intact reward processing in MDD (33), and provide contrast with paradigms which

appear to be more reliably sensitive (34, 35). Although details of the experimental design within the reinforcement learning framework may be relevant to understanding these discrepancies, it may also be that theoretical accounts of motivation that extend beyond a focus on the arrangement of stimuli, responses requirements and reinforcement contingencies may be insightful in determining why some paradigms are sensitive to differences related to depression and some are not (36).

Neurocomputational Basis

If the spirit of the impulsivity construct is one of sub-optimal decision making, then considering impulsivity in terms of the SAT might emphasize a failure to optimize RT in order to maximize utility, rather than simple premature or hasty responding. But whether or not healthy individuals show an optimal trade-off of speed and accuracy is also debated (37), and can be considered in terms of the drift diffusion model. This provides a framework to allow a derivation of optimal performance on decision paradigms across different levels of sensorimotor signal to noise ratio [SNR—(37)]. In addition, Manohar et al. (38) demonstrated that reward can provide a general improvement in performance rather than biasing toward speed or accuracy. In our data, there was a strong negative correlation between the degree of RT speeding and enhanced error rates. For a given SNR, this might be explained by proposing that individuals differ considerably regarding the relative utility of reward and punishments available on the task. For the HC and MDD groups, the pattern of findings follows what might be expected if participants showed some variation in how the response threshold parameter is set (i.e., more or less liberally) in order to promote reward rate or reduce punishment rate. It would also be necessary to propose an increase in SNR in the high reward condition [see (38)], as performance was generally better (faster and as accurate) here than in the low reward conditions. By contrast, the bipolar participants did not conform to this pattern. Both bipolar groups shortened their RTs overall in the high reward condition, suggesting a loosening of the decision threshold, but individual differences in this shortening were not always accompanied by predictable changes in error rate. It may be that some bipolar participants showed a decrease in SNR during the high reward condition. In combination with looser decision thresholds, a decrease in SNR might lead to increased error rates and shorter reaction times—the pattern seen in the BPE group. A more subtle effect of reducing SNR in the high condition might simply be to reduce the coupling between error rates and RT, which was the finding seen in the BPD group. In other words, the same type of explanation (i.e., a relative decrease in SNR in high reward conditions) might account for both the observed main effect (BPE) or the group by speeding interaction (BPD). High reward cues in the bipolar groups may affect behavior by a number of different mechanisms, including reduced selective attention, or the engagement of competing but irrelevant responses. Either possibility may appear to decrease SNR in the high reward condition.

Clearly then, our data do not support the idea that there is a simple change in response threshold in mood disorders, but previous studies which manipulated serotoninergic neurotransmission using acute tryptophan depletion (ATD) can be largely explained in this way (12, 26). Specifically, ATD was associated with a reduction in reward-related speeding, particularly in highly impulsive individuals (12) and individuals carrying the ss allele of the 5-HT transporter gene (26). In both of these studies, errors broadly tended to follow what would be expected by RT speeding: for example, ATD was associated with overall reduced error rates in ss individuals (26), and fewer errors on high compared to low reward conditions (12).

Limitations

Medication was a confound in the present study, and the presence of psychiatric control groups (e.g., MDD) did not allow us to correct for this completely: the effect seen in the BPE group (increased errors in the high vs. low condition) did not survive correction for medication load, although the effect seen in the BPD group (error by RT interaction) did. However, as the BPE group showed similar error rates if medicated by antipsychotics, mood stabilizers or higher overall doses than if they were not medicated in this way, it seems most likely that the reduction in significance relates to confounding and a consequent loss of statistical power rather than a particular effect of medication on performance. Finally, the findings of the present study do not support the contention that antidepressants improve performance which was an interpretation of our previous work (14), but it remains possible that the effect of anti-depressants may be age dependent, as described above.

One limitation of the paradigm is that it is broadly reward-focused. Recent studies have manipulated reward and punishment independently within the context of compatible motivated RT paradigms (27, 39). Future studies could usefully examine the generalization of these finding across different experimental contingencies. One straightforward manipulation would be to add another block (or more) of trials: this would allow more precise measurement of asymptotic performance, particularly of error rates which are low and thus may be difficult to estimate accurately. Finally, future studies could also explore drift diffusion modeling to verify some of our conclusions, although some more substantial alterations to the experimental design may be necessary to constrain the number of potential free parameters (40).

Summary

In summary, we emphasize two primary contributions of the present work. First, the findings confirm the presence of reward-related speeding within mood disorders: this finding is in line with our previous work, but does not support the hypothesis of motivational impairment within depressed individuals. Second, we provide evidence for an alteration in a reward-related trade-off between speed and accuracy within individuals with BD. Our favored interpretation of this finding is that individuals with BD may show a decrease in sensorimotor SNR under high reward expectation, as opposed to individuals with MDD and HC who show increased SNR. Together, the findings suggest a novel avenue for research into impulsivity in mood disorders.

AUTHOR CONTRIBUTIONS

HC was involved in the framing of the study, data analysis, and write up of the manuscript. JF was involved in data analysis and editing of the manuscript. HA and RS was involved in data collection and management. JA was involved in study design, organization, and data collection. BS was involved in study design and editing of the manuscript. MP was involved in study design, organization, framing of the study, and write up of the manuscript.

FUNDING

This study was supported by National Institute of Mental Health (NIMH) grant MH076971 (to MP).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00396/full#supplementary-material

REFERENCES

1. Muhtadie L, Johnson SL, Carver CS, Gotlib IH, Ketter TA. A profile approach to impulsivity in bipolar disorder: the key role of strong emotions. *Acta Psychiatr Scand.* (2014) 129:100–8. doi: 10.1111/acps.12136
2. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry* (2014) 171:829–43. doi: 10.1176/appi.ajp.2014.13081008
3. Nusslock R, Alloy LB. Reward processing and mood-related symptoms: an RDoC and translational neuroscience perspective. *J Affect Disord.* (2017) 216:3–16. doi: 10.1016/j.jad.2017.02.001
4. Ford BQ, Mauss IB, Gruber J. Valuing happiness is associated with bipolar disorder. *Emotion* (2015) 15:211–22. doi: 10.1037/emo0000048
5. Cooke RG, Robb JC, Young LT, Joffe RT. Well-being and functioning in patients with bipolar disorder assessed using the MOS 20-ITEM short form (SF-20). *J Affect Disord.* (1996) 39:93–7. doi: 10.1016/0165-0327(96)00016-X
6. Chase HW, Nusslock R, Almeida JR, Forbes EE, Labarbara EJ, Phillips ML. Dissociable patterns of abnormal frontal cortical activation during anticipation of an uncertain reward or loss in bipolar versus major depression. *Bipolar Disord.* (2013) 15(8):839–54. doi: 10.1111/bdi.12132
7. Balleine BW, Killcross S. Parallel incentive processing: an integrated view of amygdala function. *Trends Neurosci.* (2006) 29:272–9. doi: 10.1016/j.tins.2006.03.002
8. Chib VS, Shimojo S, O'doherty JP. The effects of incentive framing on performance decrements for large monetary outcomes: behavioral and neural mechanisms. *J Neurosci.* (2014) 34:14833–44. doi: 10.1523/JNEUROSCI.1491-14.2014
9. Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH. Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biol Psychiatry* (2008) 64:162–8. doi: 10.1016/j.biopsych.2007.12.001
10. Roiser JP, Cannon DM, Gandhi SK, Taylor Tavares J, Erickson K, Wood S, et al. Hot and cold cognition in unmedicated depressed subjects with bipolar disorder. *Bipolar Disord.* (2009) 11:178–89. doi: 10.1111/j.1399-5618.2009.00669.x
11. Adida M, Jollant F, Clark L, Besnier N, Guillaume S, Kaladjian A, et al. Trait-related decision-making impairment in the three phases of bipolar disorder. *Biol Psychiatry* (2011) 70:357–65. doi: 10.1016/j.biopsych.2011.01.018
12. Cools R, Blackwell A, Clark L, Menzies L, Cox S, Robbins TW. Tryptophan depletion disrupts the motivational guidance of goal-directed behavior as a function of trait impulsivity. *Neuropsychopharmacology* (2005) 30:1362–73. doi: 10.1038/sj.npp.1300704
13. Murray GK, Clark L, Corlett PR, Blackwell AD, Cools R, Jones PB, et al. Incentive motivation in first-episode psychosis: a behavioural study. *BMC Psychiatry* (2008) 8:34. doi: 10.1186/1471-244X-8-34
14. Chase HW, Michael A, Bullmore ET, Sahakian BJ, Robbins TW. Paradoxical enhancement of choice reaction time performance in patients with major depression. *J Psychopharmacol.* (2010) 24:471–9. doi: 10.1177/0269881109104883
15. Evenden JL. Varieties of impulsivity. *Psychopharmacology* (1999) 146:348–61. doi: 10.1007/PL00005481
16. Dickman SJ. Functional and dysfunctional impulsivity: personality and cognitive correlates. *J Pers Soc Psychol.* (1990) 58:95–102. doi: 10.1037/0022-3514.58.1.95
17. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0).* New York, NY: Biometrics Research Department, New York State Psychiatric Institute (1995).
18. Nusslock R, Almeida JR, Forbes EE, Versace A, Frank E, Labarbara EJ, et al. Waiting to win: elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar disorder adults. *Bipolar Disord.* (2012) 14:249–60. doi: 10.1111/j.1399-5618.2012.01012.x
19. Fournier JC, Chase HW, Almeida J, Phillips ML. Model specification and the reliability of fMRI results: implications for longitudinal neuroimaging studies in psychiatry. *PLoS ONE* (2014) 9:e0105169. doi: 10.1371/journal.pone.0105169
20. Fournier JC, Chase HW, Almeida J, Phillips ML. Within- and between-session changes in neural activity during emotion processing in unipolar and bipolar depression. *Biol Psychiatry Cogn Neurosci Neuroimaging* (2016) 1:518–27. doi: 10.1016/j.bpsc.2016.03.005
21. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
22. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* (1978) 133:429–35. doi: 10.1192/bjp.133.5.429
23. Spielberger CD, Gorsuch RL, Lushene R. *State-Trait Anxiety Invenstory Test Manual Form Y*. Palo Alto, CA: Consulting Psychological Press (1983).
24. Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, et al. A neural basis for general intelligence. *Science* (2000) 289:457–60. doi: 10.1126/science.289.5478.457
25. Harris CM, Waddington J, Biscione V, Manzi S. Manual choice reaction times in the rate-domain. *Front Hum Neurosci.* (2014) 8:418. doi: 10.3389/fnhum.2014.00418
26. Roiser JP, Blackwell AD, Cools R, Clark L, Rubinsztein DC, Robbins TW, et al. Serotonin transporter polymorphism mediates vulnerability to loss of incentive motivation following acute tryptophan depletion. *Neuropsychopharmacology* (2006) 31:2264–72. doi: 10.1038/sj.npp.1301084
27. Griffiths B, Beierholm UR. Opposing effects of reward and punishment on human vigor. *Sci Rep.* (2017) 7:42287. doi: 10.1038/srep42287
28. Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. *Brain* (2008) 131:2084–93. doi: 10.1093/brain/awn136
29. Gallistel CR. The importance of proving the null. *Psychol Rev.* (2009) 116:439–53. doi: 10.1037/a0015251
30. Versace A, Almeida JR, Hassel S, Walsh ND, Novelli M, Klein CR, et al. Elevated left and reduced right orbitomedial prefrontal fractional anisotropy in adults with bipolar disorder revealed by tract-based spatial statistics. *Arch Gen Psychiatry* (2008) 65:1041–52. doi: 10.1001/archpsyc.65.9.1041
31. Mueller SC, Ng P, Temple V, Hardin MG, Pine DS, Leibenluft E, et al. Perturbed reward processing in pediatric bipolar disorder: an antisaccade study. *J Psychopharmacol.* (2010) 24:1779–84. doi: 10.1177/0269881109353462

32. Dillon DG, Wiecki T, Pechtel P, Webb C, Goer F, Murray L, et al. A computational analysis of flanker interference in depression. *Psychol Med.* (2015) 45:2333–44. doi: 10.1017/S0033291715000276
33. Robinson OJ, Chase HW. Learning and choice in mood disorders: searching for the computational parameters of Anhedonia. *Comput Psychiatr.* (2017) 1:208–33. doi: 10.1162/CPSY_a_00009
34. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J Abnorm Psychol.* (2012) 121:553–8. doi: 10.1037/a0028813
35. Huys QJ, Pizzagalli DA, Bogdan R, Dayan P. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. *Biol Mood Anxiety Disord.* (2013) 3:12. doi: 10.1186/2045-5380-3-12
36. Ryan RM, Deci EL. On happiness and human potentials: a review of research on hedonic and eudaimonic well-being. *Annu Rev Psychol.* (2001) 52:141–66. doi: 10.1146/annurev.psych.52.1.141
37. Bogacz R, Hu PT, Holmes PJ, Cohen JD. Do humans produce the speed-accuracy trade-off that maximizes reward rate? *Q J Exp Psychol.* (2010) 63:863–91. doi: 10.1080/17470210903091643
38. Manohar SG, Chong TT, Apps MA, Batla A, Stamelou M, Jarman PR, et al. Reward pays the cost of noise reduction in motor and cognitive control. *Curr Biol.* (2015) 25:1707–16. doi: 10.1016/j.cub.2015.05.038
39. Crockett MJ, Clark L, Robbins TW. Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans. *J Neurosci.* (2009) 29:11993–9. doi: 10.1523/JNEUROSCI.2513-09.2009
40. Winkel J, Hawkins GE, Ivry RB, Brown SD, Cools R, Forstmann BU. Focal striatum lesions impair cautiousness in humans. *Cortex* (2016) 85:37–45. doi: 10.1016/j.cortex.2016.09.023

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 04 October 2018
doi: 10.3389/fpsyt.2018.00470

Cognitive Remediation Interventions in Schizoaffective Disorder: A Systematic Review

Ester Lopez-Fernandez[1,2†], Brisa Sole[2†], Esther Jimenez[2], Estela Salagre[2], Anna Gimenez[3], Andrea Murru[2], Caterina del Mar Bonnín[2], Benedikt Lorenz Amann[4,5,6], Iria Grande[2], Eduard Vieta[2*] and Anabel Martínez-Aran[2]*

[1] Unidad de Patología Dual, Hospital Santa Maria, Gestió de Serveis Sanitaris, Lleida, Spain, [2] Barcelona Bipolar Disorders Program, Institute of Neurosciences, IDIBAPS, CIBERSAM, Hospital Clinic, University of Barcelona, Barcelona, Spain, [3] Institute of Neurosciences, Hospital Clinic, University of Barcelona, Barcelona, Spain, [4] Centro Fórum Research Unit, CIBERSAM, Institut de Neuropsiquiatria i Addiccions, Hospital del Mar, Barcelona, Spain, [5] Department of Psychiatry, Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain, [6] Department of Psychiatry, Autonmous University Barcelona, Barcelona, Spain

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Rebecca Strawbridge,
King's College London,
United Kingdom
Andrea Fagiolini,
Università degli Studi di Siena, Italy
Muhammad Ishrat Husain,
University of Toronto, Canada

***Correspondence:**
Iria Grande
igrande@clinic.cat
Eduard Vieta
evieta@clinic.ub.es

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *26 June 2018*
Accepted: *07 September 2018*
Published: *04 October 2018*

Citation:
Lopez-Fernandez E, Sole B, Jimenez E, Salagre E, Gimenez A, Murru A, Bonnín CM, Amann BL, Grande I, Vieta E and Martínez-Aran A (2018) Cognitive Remediation Interventions in Schizoaffective Disorder: A Systematic Review. Front. Psychiatry 9:470. doi: 10.3389/fpsyt.2018.00470

Background: Patients with schizoaffective disorder (SAD) suffer from cognitive impairment, which negatively influences their functionality. Cognitive remediation (CR) interventions have been shown to be effective in patients with schizophrenia (SZ) and bipolar disorder (BD), but evidence in SAD is limited so far. The aim of this study is to systematically review the published data on CR interventions, either in neurocognition or social cognition, in patients with SAD.

Methods: We conducted a comprehensive, computerized literature search using terms related to CR interventions in psychotic and affective disorders, and particularly in SAD. Pubmed, Embase, and Web of Knowledge databases were used up to February 28th, 2018 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The search returned 2672 articles of which four were finally selected meeting the inclusion criteria.

Results: Cognitive Enhancement Therapy, computerized Cognitive Remediation Therapy and Cognitive Training showed positive results in subsamples of patients with SAD regarding neurocognition and functioning in comparable terms to patients with schizophrenia as well as in a greater extent in quality of life. Benefits in social cognition were also described when Social Cognition Interaction Training was considered in patients with SAD.

Conclusions: CR interventions seem to improve neurocognition and social cognition in patients with SAD as well as functioning and quality of life. However, further randomized controlled trials on CR interventions with an optimized design focusing on selected sample of patients with SAD are imperative.

Keywords: schizoaffective disorder, affective psychosis, cognitive enhancement, cognitive remediation, cognitive rehabilitation, cognitive training

INTRODUCTION

Cognitive impairment is highly prevalent in several mental disorders, especially in those presenting with psychotic symptoms (1–5). Therefore, a neuropsychological examination of patients with psychiatric disorders has been progressively integrated in the elementary assessment of these patients (6, 7). Cognitive impairment has been widely studied in patients with schizophrenia (SZ), who usually exhibit some cognitive dysfunction preceding the illness onset (8). The most prevalent impaired cognitive domains in these patients are attention, processing speed, working memory, and problem solving (9–11). Cognitive impairment is also common in bipolar disorder (BD) even during euthymia (12–15). Although a subgroup of patients with BD may present some mild cognitive deficits before illness onset or even a higher cognitive performance than healthy population, most patients present an average cognitive performance until the first episode (16–18). After illness onset, cognitive performance in BD declines in particular in the domains of attention, verbal learning and memory, and executive functions according to clinical severity and number of relapses (8, 13, 19). Therefore, in general terms, there are many similarities between SZ and BD including scope of cognitive domains (20, 21).

First descriptions on cognitive performance of patients with schizoaffective disorder (SAD) come from studies with mixed samples of patient with SAD and SZ (22–24). Later, comparisons on the cognitive performance between SAD and SZ were also published (25–33). On the one hand, studies suggested that both groups of patients might present a similar pattern of neurocognitive impairment, especially in memory, executive functions, cognitive flexibility, reasoning, and problem solving (25–28). On the other hand, subsequent studies described less severity of neurocognitive impairment in patients with SAD compared to patients with SZ (29–33). Concerning social cognition, patients with SAD displayed a higher performance on tasks related to the Theory of Mind (ToM) compared to patients with SZ (32). When comparing the neurocognitive performance between patients with SAD and BD, poorer execution in verbal memory and occupational functioning has been detected in patients with SAD (4). All in all, these findings evidence the cognitive heterogeneity in patients with SAD (31, 34) and place this disorder in an intermediate position in terms of cognitive performance between SZ and BD although possibly closer to SZ (35). In terms of structural neuroimaging abnormalities, SAD also resembles more SZ than BD (36).

Since cognitive impairment is related to a worse clinical course and poor functional outcome (3, 37–40), it needs to be considered as a therapeutic clinical target in order to improve both psychosocial functioning and quality of life of patients with SAD (41–44). Nowadays some studies have suggested that social cognition may explain more functional outcome variance than neurocognition and that is why social cognition has been increasingly considered as another important treatment target (45, 46). Cognitive remediation (CR) interventions in psychiatric disorders are psychological or pharmacological based approaches (42). Concerning pharmacological treatments in affective and psychotic disorders, evidence so far suggests only a small effect on cognitive improvement; several drugs with potential pro-cognitive effects are currently being investigated (47, 48). With regards to psychological approaches, CR interventions have been developed to improve cognitive processes such as attention, memory, executive function, social cognition, and metacognition (Cognitive Remediation Experts Workshop, April, 2010) (49, 50).

The evidence of CR in neurocognition and social cognition in patients with SAD mainly stems from mixed sample studies, generally of patients with SAD and SZ or in fewer cases patients with SAD and BD (51). Although there are no studies focused exclusively on analyzing the efficacy of cognitive interventions in samples composed by patients with SAD, a systematic review about cognitive rehabilitation on patients with SAD as well as affective disorders hinted an improvement on the level of cognitive performance after completion of cognitive remediation in patients with SAD (52). The data of SAD in this study were determined by estimated pooled effect size (ES) weighted for the percentage of patients with SAD. Potential changes in other outcomes apart from cognition, such as social cognition, psychosocial functioning, and quality of life were not analyzed. According to the lack of knowledge of CR interventions in patients with SAD, we aimed to systematically review the evidence on CR interventions in neurocognition, social cognition, psychosocial functioning, and quality of life in patient with SAD exclusively and describe their possible benefits in these particular patients.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (53).

Data Sources and Search Terms

A comprehensive literature search of CR interventions in SAD was conducted by three authors independently (EL, BS, and IG) using the search terms in Pubmed, Embase, and Web of Science electronic databases from inception to February 28th, 2018.

The following Boolean logic algorithms were used: In Pubmed, (schizoaffective OR schizo-affective OR "affective disorder" OR "affective psychosis" OR "bipolar" OR "manic depression" OR schizophrenia OR "schizophreniform psychosis") AND ("cognition training" OR "cognition therapy" OR "cognitive remediation" OR "cognitive training" OR "cognitive rehabilitation" OR "cognitive therapy" OR "cognitive intervention" OR "cognitive treatment" OR "neurocognitive remediation" OR "neurocognitive training" OR "neurocognitive rehabilitation" OR "neurocognitive therapy" OR "neurocognitive intervention" OR "neurocognitive treatment" OR "neuropsychological training" OR "neuropsychological rehabilitation" OR "neuropsychological therapy" OR "neuropsychological treatment" OR "metacognitive training"); and in Embase and Web of Science: "schizoaffective AND ("cognitive remediation" OR "cognitive rehabilitation" OR "cognitive training").

Reference list of individual papers were also examined to identify any additional relevant studies.

Study Inclusion Criteria

Records were reviewed using the following inclusion criteria: (1) Published studies (randomized clinical trials and follow-up cohort studies) about cognitive interventions targeted at improving cognitive skills, functioning, or quality of life which reported results about the sample or subsample of patients with SAD with at least 2 timing outcomes measures; (2) number or proportion of cases diagnosed with SAD in the sample; (3) diagnoses of SAD according to DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-9, or ICD-10; (4) no language restrictions were applied in this review; (5) no comparator group was imperative.

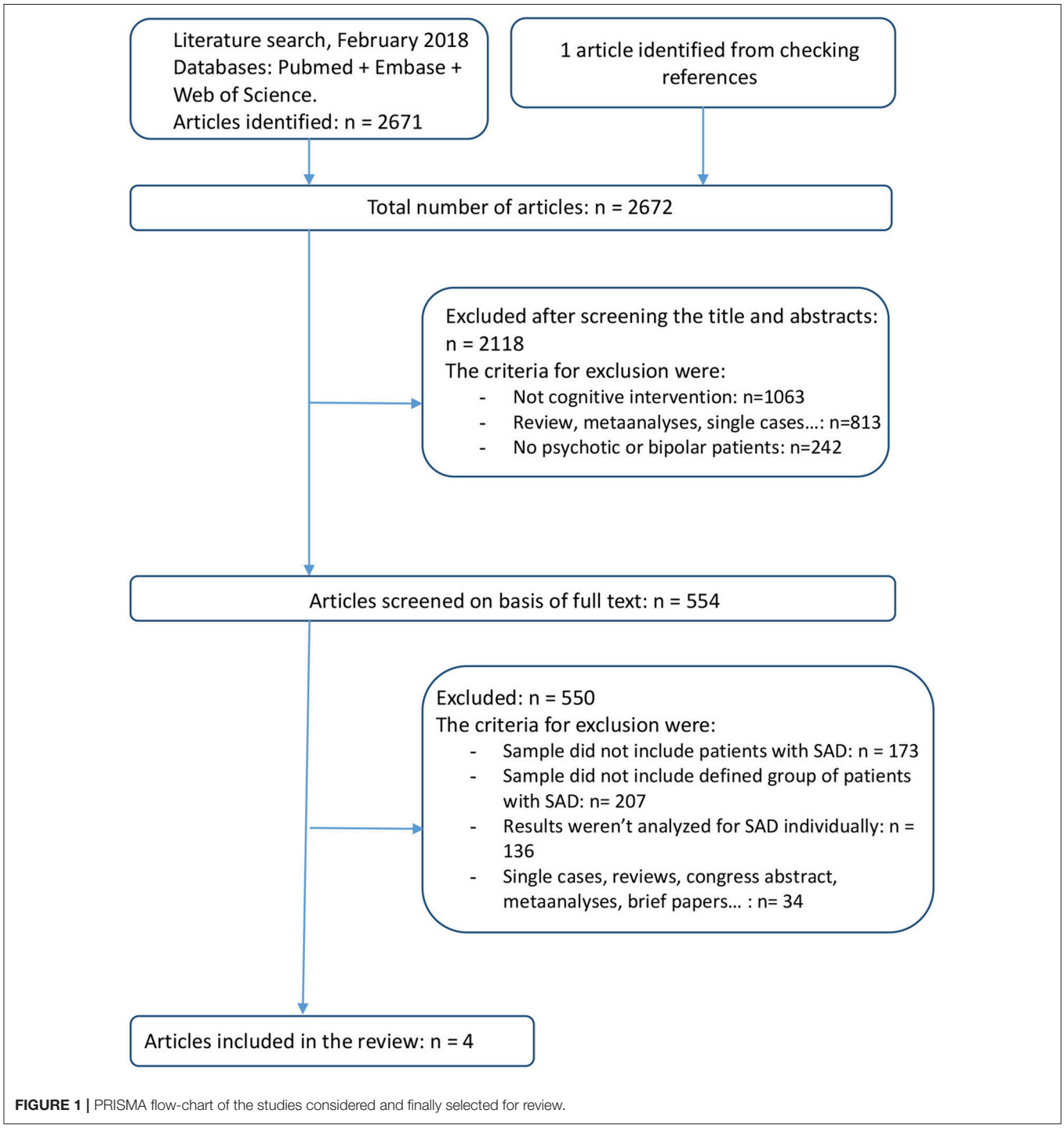

FIGURE 1 | PRISMA flow-chart of the studies considered and finally selected for review.

Study Exclusion Criteria

The exclusion criteria applied were: (1) meta-analyses, systematic or narrative reviews, single cases, cases series, study protocols, letters to the editor, editorials, debate articles, opinion papers or congress abstracts; (2) interventions not involving CR interventions; (3) trials without identifying the number of participants with SAD; (4) studies without concrete outcomes about patients with SAD.

Procedures and Data Extraction

Articles were selected based on title and abstract and, when necessary, on examination of the full text to assess its relevance. After elimination of duplicated sources, the full texts of the potentially eligible studies were considered. References were also reviewed to identify further possible studies of interest. Most existing articles on this subject about patients with psychosis and BD were reviewed, since in many cases the sample was mixed and the diagnosis of SAD was not detected in the search.

Extracted information was synthesized in two tables. In **Table 1** the characteristics of the selected studies and main results are summarized: (a) first author and year of publication; (b) characteristics of the sample: (c) sample diagnosis; (d) study design; (e) outcome measures; (f) results summary; and (g) limitations. In **Table 2** the characteristics of the interventions applied according to the following structure: (a) intervention; (b) target; (c) duration; (d) setting: individual or group intervention; and (e) type: computer assisted or non-computer assisted sessions.

RESULTS

Using the aforementioned keywords, the search returned 2672 records (**Figure 1**). The literature search identified 554 potentially relevant studies. After excluding studies that did not include or describe the sample of patients with SAD and their outcomes, four papers were identified according to the inclusion criteria (54–57).

The sample consisted of 73 patients with SAD out of 216 (**Table 1**).Two studies were performed in USA (55, 57), one in Germany (56), and one in Spain (54). The average study global sample size was 54 (SD 22.4) participants ranging from 32 to 89 patients. 58.3% of participants were men with a mean age of 38.1 ($SD = 9.2$) years. Three studies reported participants illness duration (54, 55, 57) which ranged from 3.2 to 30 years with a mean duration of 16.6 (SD 13.9) years. The average percentage of patients with SAD in the four studies was 33.8% in a range from 10.8 to 44%. The study with the largest sample of SAD was carried by Twamley et al. (57) with a sample of 39 patients. The interventions carried out in each study are described in **Table 2**.

Lewandowski et al. (55) compared a group that received Cognitive Enhancement Therapy (CET) with another group that received Enriched Supportive Therapy (EST) as a control group in a randomized controlled trial. The total sample included 20 patients with SAD and 38 with SZ. The authors conducted a secondary analysis comparing cognitive outcomes in patients with SAD and SZ with positive findings for CET in both diagnoses. The authors did not find a significant influence of the diagnosis on the relationship between improvement and treatment condition for the domains of processing speed, neurocognition, cognitive style, social cognition, social adjustment, or symptoms. Moreover, they described significant benefits for CET vs. EST for both SAD and SZ in within-group analysis: social cognition (SAD d = 1.69, SZ d = 1.68); social adjustment (SAD d = 1.36, SZ d = 1.65); and symptoms (SAD d = 1.00, SZ d = 0.68); all $p < 0.045$. In patients with SZ, CET produced significant improvement over EST in neurocognition (d = 0.46, $p = 0.025$) and cognitive style (d = 1.08, $p = 0.009$), however only trend-level effects were observed among patients with SAD (d = 0.52, $p = 0.089$ and d = 0.99, $p = 0.098$, respectively). No significant effect of the diagnosis on clinical improvement was found, with the exception of a significant reduction on depressive and anxious symptoms in patients with SAD ($p = 0.019$). This may be due to higher levels of anxiety and depression at baseline in this group of patients.

The computerized Cognitive Remediation Therapy (cCRT) is the intervention used in the study by Scheu et al. This study sample included 10 patients with SAD and 22 with SZ. After 4 weeks, the authors observed a significant improvement in the neurocognitive performance that involved attention memory, strategy, numeracy and visuo-motor skills in patients with SAD and SZ (56). No significant differences were found in improvement rates between both diagnostic groups. There was no significant correlation between improvement rates and the number of attended training sessions, but better improvement rates were linked to a higher total number of completed tasks ($r = 0.36$, $p < 0.05$). Correlation analyses revealed no significant relationship between any of the baseline cognitive or symptom measures and improvement rates. Cognitive improvements on processing speed and verbal memory were associated with higher baseline scores on the general PANSS and total PANSS ($r = -0.44$, $p < 0.05$; $r = -0.45$, $p < 0.01$, respectively), while improvements on Trail Making Test A were related to higher scores in the positive PANSS ($r = -0.43$, $p < 0.05$). Higher scores in the PANSS scores indicated worse clinical state.

Twamley et al. (57) studied the efficacy of Cognitive Training (CT) and Standard Pharmacotherapy (SP) compared to SP alone in a mixed sample of 39 patients with SAD, 45 with SZ and 5 with psychosis not otherwise specified. Patients showed a significant improvement in attention ($p = 0.049$), verbal memory ($p = 0.017$), and negative symptoms severity ($p = 0.002$) at 3-month follow-up and in verbal memory ($p = 0.039$), prospective memory ($p = 0.050$), functional capacity ($p = 0.004$), negative symptoms severity ($p = 0.025$), and self-reported quality of life ($p = 0.004$) at 6-month follow-up. Results of cognitive outcomes were not available according to diagnoses. However, patients with SAD showed a significant improvement in subjective perception of quality of life at 6 months compared to patients with SZ ($p = 0.03$) (57). At 3-month follow-up, improvement in digit span forward and in Hopkins Verbal Learning Test (HVLT) were associated with higher levels of negative symptoms severity at baseline ($r = 0.45$, $p = 0.045$; $r = 0.50$, $p = 0.025$, respectively). Moreover, improvement in

TABLE 1 | Characteristics of the studies selected on Cognitive Remediation interventions in schizoaffective disorder.

Study	Sample characteristics	Sample diagnosis (n)	Design	Outcome measures	Results summary	Limitations
Lahera et al. (54)	37 outpatients Age = 39.2 (10.4) years old Gender = 64.9% female Illness = 13.3 (7.8) years	BDI = 28 BDII = 5 SAD = 4	SCIT vs. TAU *n* = 21/16 SAD: 14.3% /6.3% Quasi-experimental study	**Social cognition** Emotion cognition: FEIT and FEDT Emotion recognition: ER40 ToM: Hinting task Social cognitive biases: AIHQ **Psychosocial functioning**: FAST and GAF	Significant group effects on every social cognitive outcome measure except for the AIHQ Intentionality subscale. No evidence of effects on aggressive attributional biases or on global functioning. Similar pattern of results with SAD excluded except no longer a significant group effect on AIHQ Intentionality or FEIT scores.	Quasi-experimental design (5 subjects reassigned after random) Heterogeneous sample No follow-up assessment
Lewandowski et al. (8)	58 outpatients Age= 25.9 (6.3) years old Gender = 31.0% female Illness = 3.2 (2.2) years	SZ = 38 SAD = 20 (12 depressed type, 8 bipolar type)	CET vs. EST *n* = 31/27 SAD: 32.3%/37.0% Subanalysis of RCT	**Processing speed:** Simple reaction time, choice reaction time and Visual-spatial scanning **Neurocognition:** WMS-R, California Verbal Learning Test, WAIS-R, TMT B, Wisconsin card sorting test, Tower of London, Neurological evaluation scale **Cognitive style:** Cognitive style and social cognition eligibility interview, Cognitive styles inventory **Social cognition:** Mayer-Salovey-Caruso Emotional Intelligence Test, social cognition profile, Cognitive style and social cognition eligibility interview **Social adjustment:** Social adjustment scale-II, Major role inventory, Global assessment scale, performance potential inventory, DHHS	SZ and SAD improved in multiple neurocognitive and social cognition domains after CET. Diagnosis did not significantly moderate this improvement. SAD had less improvement on neurocognition and cognitive style than SZ. No significant effects in processing speed. SAD groups exhibited significantly greater improvement on symptoms, specifically on depression and anxiety.	Small sample and unequal between groups Diagnostic stability was unclear in the sample (some patients changed symptoms over the study period)
Scheu et al. (56)	32 in- and outpatients Age = 33.4 (10.4) years old Gender = 46.9% female	SZ = 22 SAD = 10	cCRT (CogPack). 70 CogPack-tasks Retrospective study	**CRT response:** % of improved tasks based on the amount of completed tasks without initial ceiling effects. **Verbal intelligence:** MWT-B **Attention**: Test d2, parameter concentration performance (KL) **Verbal memory:** RBMT **Processing speed and executive functioning:** TMT	The improvement rate was 68% (improved tasks based on the amount of completed tasks without initial ceiling effects). No significant differences between SZ and SAD. No significant relationship between any of the baseline cognitive or symptom measures and improvement rates.	No control group Small sample Dichotomous primary outcomes Tasks assessment only three times

(Continued)

TABLE 1 | Continued

Study	Sample characteristics	Sample diagnosis (n)	Design	Outcome measures	Results summary	Limitations
					Better baseline cognition was associated with a higher percentage of tasks with initial ceiling effects. Improvement from baseline to the second assessment after 4 weeks on all neurocognitive functions. Greater improvement in poor cognitive performance or higher values on the PANSS scores at baseline.	
Twamley et al. (57)	89 outpatients 51 study completers Age = 47.3 (9.8) years old Gender = 35% female Illness = 25.4 (19.2) years	SZ = 45 SAD = 39 PNOS = 5	CT+SP vs. SP Subanalysis of RCT	**Prospective memory**: MIST, **Attention and vigilance**: WAIS-III **Verbal Learning and memory**: HVLT-R **Executive functioning:** WCST-64 **Quality of life**: QOLI. **Functional capacity:** UPSA **Cognitive insight**: Beck Cognitive Insight Scale	CT associated improvement was correlated with worse baseline scores on measures of cognitive performance, symptom severity, functional capacity, and self-rated quality of life, cognitive problems, and strategy use. SAD got more improvement than SZ in subjective quality of life at 6 months.	Small sample Passive control group was treatment as usual No previous measures of motivation or cognitive improvement insight

AIHQ, Ambiguous Intentions Hostility Questionnaire; BD, Bipolar Disorder; BDI, Bipolar Disorder Type I; BDII, Bipolar Disorder Type 2; CET, Cognitive Enhancement Therapy; cCRT, Computerized Cognitive Remediation Therapy; CT, Cognitive Training; d2, Aufmerksamkeits-Belastungs-Test; DHHS, Department of Health and Human Services; ER40, Emotion Recognition; EST, Enriched Supportive Therapy; FAST, Functioning Assessment Short Test; FEDT, Face Emotion Discrimination Test; FEIT, Face Emotion Identification Task; GAF, Global Assessment of Functioning scale; HVLT-R, Hopkins Verbal Learning Test-Revised; KL, Concentration Performance value; MIST, Memory for Intentions Screening Test; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest test B; PNOS, Psychosis Non Specified; QOLI, Quality of life; RBMT, Rivermead Behavioral Memory Test; RCT, Randomized Controlled Trial; SCIT, Social Cognition and Interaction Training; SD, Standard Desviation; SP, Standard Pharmacotherapy; SZ, Schizophrenia; SAD, Schizoaffective disorder; TAU, Treatment As Usual; TMT, Trail Making Test; TMT A, Trail Making Test A; TMT B, Trail Making Test B; ToM, Theory of Mind; UPSA, University of California Performance-Based Skills Assessment; WAIS-III, Wechsler Adult Intelligence Scale Third Edition; WAIS-R, Wechsler Adult Intelligence Scale-Revised; WCST-64, Wisconsin Card Sorting Test-64 Card Version; WMS-R, Wechsler Memory Scale-Revised.

TABLE 2 | Description of the studied Cognitive Remediation interventions in schizoaffective disorder.

Intervention	Target	Duration	Setting	Type
Cognitive Enhancement Therapy (CET)	Cognitive functions and social cognition	Biweekly sessions (60 h cognitive training + 45 h social cognition) for 24 months	Individual/group	Computer assisted and non-computer assisted sessions
computerized Cognitive Remediation Therapy cCRT (CogPack)	Cognitive function	50 min sessions twice a week over a maximum period of 8 weeks	Individual	Computer assisted
Cognitive Training (CT)	Cognitive function	2 h once a week for 12 weeks	Group	Non-computer assisted
Social Cognition and Interaction Training (SCIT)	Social cognition	1 h once a week for 18 weeks	Group	Non-computer assisted

digit span was related to higher levels of self-reported cognitive problems ($r = 0.48$, $p = 0.033$). An improvement in HVLT percent retention at 3 months was also associated with lower cognitive strategy use at baseline ($r = -0.48$, $p = 0.033$). At 6-month follow-up, improvement on the University of California, San Diego, Performance-Based Skills Assessment (UPSA) functional capacity was associated with higher levels of positive symptoms ($r = 0.45$, $p = 0.035$), lower levels of cognitive strategy use ($r = -0.54$, $p = 0.009$), and worse UPSA performance at baseline ($r = -0.56$, $p = 0.007$).

Lahera et al. (54) described the benefits of Social Cognition and Interaction Training (SCIT) compared to Treatment As Usual (TAU) in a mixed sample of 4 patients with SAD and 33 with BD. The authors detected a significant improvement in the group that received SCIT on each social cognitive outcome except for the Ambiguous Intentions Hostility Questionnaire (AIHQ) Intentionality subscale, with a trend to significance ($p = 0.069$). The group that received SCIT showed a significant improvement in emotion perception and ToM ($p < 0.05$), and significant improvement in hostile attribution biases compared to the TAU group ($p < 0.05$). The SCIT group showed a within-group improvement on the AIHQ Blame subscale ($d = -0.19$, $p < 0.01$), an improvement in AIHQ Hostility Bias ($d = -0.55$, $p < 0.05$), an improvement in scores on the Hinting Task ($d = 0.4$, $p < 0.05$), an improvement on the Emotion Recognition-40 (ER40) ($d = 0.51$, $p < 0.05$), and an improvement on the Face Emotion Discrimination Task (FEDT) ($d = 0.67$, $p < 0.01$) and Face Emotion Identification Task (FEIT) ($d = 0.81$, $p < 0.05$). *Post-hoc* analysis did not evidence an effect of diagnoses on the results. No evidence for between-group effects on any clinical outcome was found.

The risk of bias was assessed in all eligible studies as recommended by the Cochrane Collaboration (58). However it was difficult to determine due to the heterogeneity of the study design and because the focus of this systematic review was beyond the main objectives of the selected articles.

DISCUSSION

Despite the scarce number of studies on the topic, there is evidence, although limited, of the effectiveness of CR interventions in patients with SAD. CET, cCRT, and CT showed positive results in cognition in the subsample of patients with SAD considering neurocognitive or functional parameters as well as outcomes related to quality of life. Benefits in social cognition were also described when SCIT as well as CET were considered in patients with SAD.

These results are in line with previous bibliography on the issue. Regarding neurocognition, Anaya et al. (52) described in their meta-analysis that CR interventions showed positive effects on cognition at post-intervention in patients with SAD as well as in patients with affective disorders with an ES of 0.32. Interestingly, the authors pointed out that the effect of CR interventions increased when the meta-analysis was limited to studies that included exclusively patients with SAD, obtaining a pooled ES weighted for the percentage of patients with SAD of 0.41. In addition, we also have found some evidence that schizoaffective patients could improve in specific measures of social cognition, social adjustment, symptoms and quality of life after receiving a CR intervention.

It is worth commenting on the studies that presented a relevant percentage of patients with SAD in the sample but did not specifically mention results of the subsample of patients with SAD. Considering neurocognition, In a subsequent article (59) of the one included in this systematic revision, Twamley et al. described general improvement in cognitive domains considering the entire sample. In another study with 53% of the sample diagnosed with SAD (60), computer-assisted cognitive rehabilitation showed greater improvement in neurocognitive performance, specifically in verbal memory and attention, and negative symptoms compared to a wait-list control group. Regarding social cognition, a recent systematic review that included studies with samples of patients with SAD and SZ (61) stated that interventions in social cognition could improve several domains related to affect recognition, ToM and social perception. However, the effect on attributional style and the relationship between improvement in social cognition and functioning were unclear. All in all, CR interventions in neurocognition and social cognition seem to be effective in the psychotic spectrum.

Whether patients diagnosed with SAD benefit from CR interventions more than SZ or less than BD is still open to question. Lewandowski et al. published the results of CET between patients with SAD and SZ in a subanalysis of a previous

study (55, 62). Although positive results were described in both groups, a lower benefit of the treatment was observed in the cognitive performance of patients with SAD compared to those with SZ. This may be due to a ceiling effect since patients diagnosed with SZ present more cognitive impairment compared to patients diagnosed with SAD. The evidence suggests that the wider the cognitive impairment at baseline, the greater benefits can be obtained with CR interventions. It may be due to the fact that there is more room for improvement or because of an increased motivation (57). Nevertheless, in the study performed by Scheu et al. (56), outcomes of patients with SAD did not differ from those observed in patient with SZ, being positive in both disorders. Thus, despite the cognitive heterogeneity (31, 34), SAD may be placed in an intermediate position in terms of neurocognitive performance between SZ and BD although possibly closer to SZ (35).

There is controversy about how basal clinical state may impact on the results of CR and how CR may influence the clinical state. With regard to the former, on one hand, Wykes et al. (63) reported in a meta-analysis focused on CR in patients with SZ that the benefits were more significant in less symptomatic patients. On the other hand, Twamley et al. (57) found an association between higher levels of negative symptoms and greater benefits, and between higher levels of positive symptoms and greater improvement in functional capacity. Therefore, they consider that the presence or severity of symptoms should not be an exclusion criterion for these interventions. Other authors consider that the severity of positive or negative symptoms does not predict the rate of improvement (19, 56, 64). Considering the latter, the two meta-analyses by Wykes et al. and McGurk et al. (63, 65) described a significant positive effect of CR on both symptoms and functionality in patients with SZ. Lewandowski et al. (55) detected greater improvement in symptoms after receiving CET in patients diagnosed with SAD compared to patients diagnosed with SZ, specifically in anxious and depressive symptoms.

Another issue of debate is the right moment to provide CR interventions. Some authors suggest that the younger the patients, the more they benefit from CR interventions (63, 66–68, 70). On the contrary, the two major meta-analysis in the literature about CR interventions concluded no relationship between these two variables or that the older the patients, the better outcomes of CR interventions (63, 65). Twamley et al. pointed out that older patients achieved more improvement, specifically in prospective memory (57). The concept of cognitive reserve may provide an explanation for the discrepancy in these results since it reflects the capacity of the brain to endure neuropathology and successfully complete cognitive tasks (69). Moreover, cognitive reserve has been found as a significant predictor of cognitive and psychosocial functioning in patients with SZ and BD (70–72). Another key issue in CR interventions relates to the relationship between number of sessions and the obtained benefits. The meta-analysis carried out by Wykes et al. (63) and the study of Scheu et al. (56) did not reveal any association between the aforementioned variables. Last but not least, the drop-out ratio is another matter of concern in CR interventions. Twamley et al. (57) analyzed who was more likely to drop out in their randomized controlled trial of CT in which 57.30% of the patients completed the therapy while 31.46% did not start it and 11.24% withdrew. Those who completed CT had more formal education and lower antipsychotic doses than had dropouts with no CT exposure, but the groups did no otherwise differ. In Lewandowski et al. (55) and Lahera et al. (54) studies, the frequencies of dropouts were 20.6 and 19.1%, respectively.

As a summary, Lewandowski et al. (55) obtained small effects on neurocognition in the group of SAD, vs. medium effects in the group of SZ. However, patients with SAD improved more in symptomatology after cognitive treatment. In this study, a similar improvement in the functionality of both groups was obtained. On the other hand, Scheu et al. (56) did not find differences in improvement rates when comparing patients with SAD and SZ. Lahera et al. (54) did not find differences after treatment when compared patients with SAD and BD, considering that the sample included four patients with SAD. Twamley et al. (57) did not report group differences but more improvement in subjective quality of life at 6 months in SAD compared to patient with SZ.

Despite data gathered in this systematic review seems to support a positive effects of CR interventions in SAD, these results should be interpreted with caution. First of all, the samples of the four reviewed studies are restricted to small subsamples of patients diagnosed with SAD within a wider sample of patients diagnosed mostly with SZ or BD. Although we only consider articles that studied the concrete subsample of SAD, the obtained results stem from *post-hoc* analyses, which are not always aligned with the aim of the primary objective of the study and therefore may increase false positive results. Moreover, the heterogeneity of the design of the reviewed CR interventions should be beared in mind. This heterogeneity could partly explain discrepancies among results from these studies.

In this systematic review, scarce studies on CR interventions in SAD were found. However, available data support that CR interventions may improve neurocognition and social cognition in this group of patients. Subsequently, functioning and quality of life on this population may also benefit from improving the daily life of patients with SAD. So as to confirm this hypothesis, further randomized controlled trials on CR interventions with an optimized design and selected sample of patients with SAD are urged.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

CMB would like to thank the Departament de Salut de la Generalitat de Catalunya for the PERIS grant (SLT002/16/00331).

IG is supported by the Instituto de Salud Carlos III, Ministry of Economy and Competitiveness of Spain [Juan Rodés Contract (JR15/00012) and a grant (PI16/00187)] integrated into the Plan Nacional de I+D+I and cofunded by ISCIII-Subdirección

General de Evaluación and Fondo Europeo de Desarrollo Regional (FEDER).

EV thanks the support of the Spanish Ministry of Economy and Competitiveness (PI15/00283) integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365) and the project SLT006/17/00357, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

AM-A thanks the support of the Spanish Ministry of Economy and Competitiveness (PI15/00330) integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM) and the project SLT006/17/00177, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

REFERENCES

1. Albus M, Hubmann W, Wahlheim C, Sobizack N, Franz U, Mohr F. Contrasts in neuropsychological test profile between patients with first-episode schizophrenia and first-episode affective disorders. *Acta Psychiatr Scand*. (1996) 94:87–93.
2. Zubieta JK, Huguelet P, O'Neil RL, Giordani BJ. Cognitive function in euthymic bipolar I disorder. *Psychiatry Res*. (2001) 102:9–20. doi: 10.1016/S0165-1781(01)00242-6
3. Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord*. (2004) 6:224–32. doi: 10.1111/j.1399-5618.2004.00111.x
4. Torrent C, Martínez-Arán A, Amann B, Daban C, Tabarés-Seisdedos R, González-Pinto A, et al. Cognitive impairment in schizoaffective disorder: a comparison with non-psychotic bipolar and healthy subjects. *Acta Psychiatr Scand*. (2007) 116:453–60. doi: 10.1111/j.1600-0447.2007.01072.x
5. Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Faerden A, et al. Neurocognitive dysfunction in bipolar and schizophrenia spectrum disorders depends on history of psychosis rather than diagnostic group. *Schizophr Bull*. (2011) 37:73–83. doi: 10.1093/schbul/sbp034
6. Miskowiak K, Burdick K, Martinez-Aran A, Bonnin CM, Bowie CR, Carvalho AF, et al. Methodological recommendations for cognition trials in bipolar disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force. *Bipolar Disord*. (2017) 19:614–26. doi: 10.1111/bdi.12534
7. Miskowiak K, Burdick K, Martinez-Aran A, Bonnin CM, Bowie CR, Carvalho AF, et al. Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. *Bipolar Disord*. (2018) 20:184–94. doi: 10.1111/bdi.12595
8. Lewandowski KE, Cohen BM, Öngur D. Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychol Med*. (2011) 41:225–41. doi: 10.1017/S0033291710001042
9. Dickinson D, Ramsey ME, Gold JM. Overlooking the Obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry* (2007) 64:532. doi: 10.1001/archpsyc.64.5.532
10. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* (1998) 12:426–45.
11. Palmer BW, Dawes SE, Heaton RK. What Do we know about neuropsychological aspects of schizophrenia? *Neuropsychol Rev*. (2009) 19:365–84. doi: 10.1007/s11065-009-9109-y
12. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*. (2006) 93:105–15. doi: 10.1016/j.jad.2006.02.016
13. Bourne C, Aydemir O, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JT, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand*. (2013) 128:149–62. doi: 10.1111/acps.12133
14. Bortolato B, Miskowiak K, Köhler CA, Vieta E, Carvalho AF. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat*. (2015) 11:3111–25. doi: 10.2147/NDT.S76700
15. Mann-Wrobel MC, Carreno JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disord*. (2011) 13:334–42. doi: 10.1111/j.1399-5618.2011.00935.x
16. Martino DJ, Samamé C, Ibañez A, Strejilevich SA. Neurocognitive functioning in the premorbid stage and in the first episode of bipolar disorder: a systematic review. *Psychiatry Res*. (2015) 226:23–30. doi: 10.1016/j.psychres.2014.12.044
17. Mollon J, David AS, Zammit S, Lewis G, Reichenberg A. Course of cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry* (2018) 75:270–9. doi: 10.1001/jamapsychiatry.2017.4327
18. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. *Nat Rev Dis Prim*. (2018) 4:18008. doi: 10.1038/nrdp.2018.8
19. Kurtz MM, Gerraty RT. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology* (2009) 23:551–62. doi: 10.1037/a0016277
20. Bora E, Yücel M, Pantelis C. Cognitive impairment in affective psychoses: a meta-analysis. *Schizophr Bull*. (2010) 36:112–25. doi: 10.1093/shbul/sbp093
21. Martínez-Arán A, Penadés R, Vieta E, Colom F, Reinares M, Benabarre A, et al. Executive function in patients with remitted bipolar disorder and schizophrenia and its relationship with functional outcome. *Psychother Psychosom*. (2002) 71:39–46. doi: 10.1159/000049342
22. Breier A, Schreiber JL, Dyer J, Pickar D. National Institute of Mental Health longitudinal study of chronic schizophrenia. Prognosis and predictors of outcome. *Arch Gen Psychiatry* (1991) 48:239–46.
23. Brekke JS, Raine A, Ansel M, Lencz T, Bird L. Neuropsychological and psychophysiological correlates of psychosocial functioning in schizophrenia. *Schizophr Bull*. (1997) 23:19–28.
24. Lysaker PH, Bryson GJ, Davis LW, Bell MD. Relationship of impaired processing speed and flexibility of abstract thought to improvements in work performance over time in schizophrenia. *Schizophr Res*. (2005) 75:211–8. doi: 10.1016/j.schres.2004.09.014
25. Manschreck TC, Maher BA, Beaudette SM, Redmond DA. Context memory in schizoaffective and schizophrenic disorders. *Schizophr Res*. (1997) 26:153–61.
26. Evans JD, Heaton RK, Paulsen JS, McAdams LA, Heaton SC, Jeste DV. Schizoaffective disorder: a form of schizophrenia or affective disorder? *J Clin Psychiatry* (1999) 60:874–82.
27. Gooding DC, Tallent KA. Spatial working memory performance in patients with schizoaffective psychosis versus schizophrenia: a tale of two disorders? *Schizophr Res*. (2002) 53:209–18. doi: 10.1016/S0920-9964(01)00258-4
28. Reichenberg A, Weiser M, Rabinowitz J, Caspi A, Schmeidler J, Mark M, et al. A population-based cohort study of premorbid intellectual, language, and behavioral functioning in patients with schizophrenia, schizoaffective disorder, and nonpsychotic bipolar disorder. *Am J Psychiatry* (2002) 159:2027–35. doi: 10.1176/appi.ajp.159.12.2027
29. Gruber O, Gruber E, Falkai P. Articulatory rehearsal in verbal working memory: a possible neurocognitive endophenotype that differentiates between

schizophrenia and schizoaffective disorder. *Neurosci Lett*. (2006) 405:24–8. doi: 10.1016/j.neulet.2006.06.062
30. Heinrichs RW, Ammari N, McDermid Vaz S, Miles AA. Are schizophrenia and schizoaffective disorder neuropsychologically distinguishable? *Schizophr Res*. (2008) 99:149–54. doi: 10.1016/j.schres.2007.10.007
31. Goldstein G, Shemansky WJ, Allen DN. Cognitive function in schizoaffective disorder and clinical subtypes of schizophrenia. *Arch Clin Neuropsychol*. (2005) 20:153–9. doi: 10.1016/j.acn.2004.03.008
32. Stip E, Sepehry AA, Prouteau A, Briand C, Nicole L, Lalonde P, et al. Cognitive discernible factors between schizophrenia and schizoaffective disorder. *Brain Cogn*. (2005) 59:292–5. doi: 10.1016/j.bandc.2005.07.003
33. Fiszdon JM, Richardson R, Greig T, Bell MD. A comparison of basic and social cognition between schizophrenia and schizoaffective disorder. *Schizophr Res*. (2007) 91:117–21. doi: 10.1016/j.schres.2006.12.012
34. Bora E, Yucel M, Pantelis C. Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. *Br J Psychiatry J Ment Sci*. (2009) 195:475–82. doi: 10.1192/bjp.bp.108.055731
35. Madre M, Canales-Rodríguez EJ, Ortiz-Gil J, Murru A, Torrent C, Bramon E, et al. Neuropsychological and neuroimaging underpinnings of schizoaffective disorder: a systematic review. *Acta Psychiatr Scand*. (2016) 134:16–30. doi: 10.1111/acps.12564
36. Amann BL, Canales-Rodríguez EJ, Madre M, Radua J, Monte G, Alonso-Lana S, et al. Brain structural changes in schizoaffective disorder compared to schizophrenia and bipolar disorder. *Acta Psychiatr Scand*. (2016) 133:23–33. doi: 10.1111/acps.12440
37. Medalia A, Richardson R. What predicts a good response to cognitive remediation interventions? *Schizophr Bull*. (2005) 31:942–53. doi: 10.1093/schbul/sbi045
38. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. (2000) 26:119–36. doi: 10.1093/oxfordjournals.schbul.a033430
39. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res*. (2004) 72:41–51. doi: 10.1016/j.schres.2004.09.009
40. Horan WP, Kern RS, Tripp C, Hellemann G, Wynn JK, Bell M, et al. Efficacy and specificity of Social Cognitive Skills Training for outpatients with psychotic disorders. *J Psychiatr Res*. (2011) 45:1113–22. doi: 10.1016/j.jpsychires.2011.01.015
41. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet* (2016) 387:1561–72. doi: 10.1016/S0140-6736(15)00241-X
42. Solé B, Jiménez E, Torrent C, Reinares M, Bonnin CDM, Torres I, et al. Cognitive impairment in bipolar disorder: treatment and prevention strategies. *Int J Neuropsychopharmacol*. (2017) 20:670–80. doi: 10.1093/ijnp/pyx032
43. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectr*. (2014) 19(Suppl. 1):38–52, 53. doi:10.1017/S1092852914000601.
44. Bonnín CM, Yatham LN, Michalak EE, Martínez-Arán A, Dhanoa T, Torres I, et al. Psychometric properties of the well-being index (WHO-5) spanish version in a sample of euthymic patients with bipolar disorder. *J Affect Disord*. (2018) 228:153–9. doi: 10.1016/j.jad.2017.12.006
45. Fett A-KJ, Viechtbauer W, Dominguez M-G, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev*. (2011) 35:573–88. doi: 10.1016/j.neubiorev.2010.07.001
46. Green MF, Olivier B, Crawley JN, Penn DL, Silverstein S. Social cognition in schizophrenia: recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. *Schizophr Bull*. (2005) 31:882–7. doi: 10.1093/schbul/sbi049
47. Salagre E, Solé B, Tomioka Y, Fernandes BS, Hidalgo-Mazzei D, Garriga M, et al. Treatment of neurocognitive symptoms in unipolar depression: a systematic review and future perspectives. *J Affect Disord*. (2017) 221:205–21. doi: 10.1016/j.jad.2017.06.034
48. Vieta E, Salagre E, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early intervention in bipolar disorder. *Am J Psychiatry* (2018) 175:411–26. doi: 10.1176/appi.ajp.2017.17090972
49. Cella M, Reeder C, Wykes T. Group cognitive remediation for schizophrenia: exploring the role of therapist support and metacognition. *Psychol Psychother Theor*. (2016) 89:1–14. doi: 10.1111/papt.12062
50. Twamley EW, Jeste D V, Bellack AS. A review of cognitive training in schizophrenia. *Schizophr Bull*. (2003) 29:359–82. doi: 10.1093/oxfordjournals.schbul.a007011
51. Murru A, Pacchiarotti I, Nivoli AMA, Grande I, Colom F, Vieta E. What we know and what we don't know about the treatment of schizoaffective disorder. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. (2011) 21:680–90. doi: 10.1016/j.euroneuro.2011.03.001
52. Anaya C, Martinez Aran A, Ayuso-Mateos JL, Wykes T, Vieta E, Scott J. A systematic review of cognitive remediation for schizo-affective and affective disorders. *J Affect Disord*. (2012) 142:13–21. doi: 10.1016/j.jad.2012.04.020
53. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (2009) 339:b2535. doi: 10.1371/journal.pmed.1000097
54. Lahera G, Benito A, Montes JM, Fernández-Liria A, Olbert CM, Penn DL. Social cognition and interaction training (SCIT) for outpatients with bipolar disorder. *J Affect Disord*. (2013) 146:132–36. doi: 10.1016/j.jad.2012.06.032
55. Lewandowski KE, Eack SM, Hogarty SS, Greenwald DP, Keshavan MS. Is cognitive enhancement therapy equally effective for patients with schizophrenia and schizoaffective disorder? *Schizophr Res*. (2011) 125:291–4. doi: 10.1016/j.schres.2010.11.017
56. Scheu F, Aghotor J, Pfueller U, Moritz S, Bohn F, Weisbrod M, et al. Predictors of performance improvements within a cognitive remediation program for schizophrenia. *Psychiatry Res*. (2013) 209:375–80. doi: 10.1016/j.psychres.2013.04.015
57. Twamley EW, Burton CZ, Vella L. Compensatory cognitive training for psychosis: who benefits? who stays in treatment? *Schizophr Bull*. (2011) 37(Suppl. 2):S55–62. doi: 10.1093/schbul/sbr059
58. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* (2011) 343:d5928. doi: 10.1136/bmj.d5928
59. Twamley EW, Vella L, Burton CZ, Heaton RK, Jeste DV. Compensatory cognitive training for psychosis. *J Clin Psychiatry* (2012) 73:1212–9. doi: 10.4088/JCP.12m07686
60. Bellucci DM, Glaberman K, Haslam N. Computer-assisted cognitive rehabilitation reduces negative symptoms in the severely mentally ill. *Schizophr Res*. (2003) 59:225–32. doi: 10.1016/S0920-9964(01)00402-9
61. Grant N, Lawrence M, Preti A, Wykes T, Cella M. Social cognition interventions for people with schizophrenia: a systematic review focussing on methodological quality and intervention modality. *Clin Psychol Rev*. (2017) 56:55–64. doi: 10.1016/j.cpr.2017.06.001
62. Eack SM, Greenwald DP, Hogarty SS, Cooley SJ, DiBarry AL, Montrose DM, et al. Cognitive enhancement therapy for early-course schizophrenia: effects of a two-year randomized controlled trial. *Psychiatr Serv*. (2009) 60:1468–76. doi: 10.1176/ps.2009.60.11.1468
63. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A Meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry* (2011) 168:472–85. doi: 10.1176/appi.ajp.2010.10060855
64. Fiszdon JM, Cardenas AS, Bryson GJ, Bell MD. Predictors of remediation success on a trained memory task. *J Nerv Ment Dis*. (2005) 193:602–8. doi: 10.1097/01.nmd.0000177790.23311.ba
65. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A Meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry* (2007) 164:1791–802. doi: 10.1176/appi.ajp.2007.07060906

66. Barlati S, Deste G, De Peri L, Ariu C, Vita A. Cognitive remediation in schizophrenia: current status and future perspectives. *Schizophr Res Treat*. (2013) 2013:156084. doi: 10.1155/2013/156084
67. Kurtz MM, Moberg PJ, Gur RC, Gur RE. Approaches to cognitive remediation of neuropsychological deficits in schizophrenia: a review and meta-analysis. *Neuropsychol Rev*. (2001) 11:197–210. doi: 10.1023/A:1012953108158
68. Tomioka Y, Jiménez E, Salagre E, Arias B, Mitjans M, Ruiz V, et al. Association between genetic variation in the myo-inositol monophosphatase 2 (IMPA2) gene and age at onset of bipolar disorder. *J Affect Disord*. (2018) 232:229–36. doi: 10.1016/j.jad.2018.02.002
69. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. (2012) 11:1006–12. doi: 10.1016/S1474-4422(12)70191-6
70. Grande I, Sanchez-Moreno J, Sole B, Jimenez E, Torrent C, Bonnin CM, et al. High cognitive reserve in bipolar disorders as a moderator of neurocognitive impairment. *J Affect Disord*. (2017) 208:621–7. doi: 10.1016/j.jad.2016.10.012
71. Anaya C, Torrent C, Caballero FF, Vieta E, Bonnin C del M, Ayuso-Mateos JL. Cognitive reserve in bipolar disorder: relation to cognition, psychosocial functioning and quality of life. *Acta Psychiatr Scand*. (2016) 133:386–98. doi: 10.1111/acps.12535
72. Amoretti S, Cabrera B, Torrent C, Mezquida G, Lobo A, González-Pinto A, et al. Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis. *Acta Psychiatr Scand*. (2018). doi: 10.1111/acps.12949. [Epub ahead of print].

Conflict of Interest Statement: IG has served as a consultant for Ferrer, advisor for Lundbeck, Otsuka and has been a speaker for Ferrer, Janssen and Lundbeck, Otsuka. EV has received grants and served as a consultant, advisor, or CME speaker for the following entities: AB-Biotics, Allergan, AstraZeneca, Bristol-Myers-Squibb, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefonica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (Centro de Investigación Biomédica en Red de Salud Mental), the Seventh European Framework Programme (European Network of Bipolar Research Expert Centres), and the Stanley Medical Research Institute.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RS and handling editor declared their shared affiliation at time of review.

frontiers in Psychiatry

PERSPECTIVE
published: 08 October 2018
doi: 10.3389/fpsyt.2018.00490

Does Cognitive Dysfunction in Bipolar Disorder Qualify as a Diagnostic Intermediate Phenotype?—A Perspective Paper

Lars Vedel Kessing[1]* *and Kamilla Miskowiak*[1,2]

[1] Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, University Hospital of Copenhagen and University of Copenhagen, Copenhagen, Denmark, [2] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

The present perspective paper addresses and discusses whether cognitive dysfunction in bipolar disorder qualifies as a diagnostic intermediate phenotype using the Robin and Guze criteria of diagnostic validity. The paper reviews current data within (1) delineation of the clinical intermediate phenotype, (2) associations of the intermediate phenotype with para-clinical data such as brain imaging and blood-based data, (3) associations to family history / genetics, (4) characteristics during long-term follow-up, and (5) treatment effects on cognition. In this way, the paper identifies knowledge gaps and suggests recommendations for future research within each of the five areas. Based on the current state of knowledge, we conclude that cognitive dysfunction does not qualify as a diagnostic intermediate phenotype or endophenotype for bipolar disorder, although promising new evidence points to emotion and reward processing abnormalities as possible putative endophenotypes.

Keywords: cognition, cognitive dysfunction, bipolar disorder, unipolar disorder, schizophrenia, intermediate phenotype, endophenotype

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Mirko Manchia,
Università degli Studi di Cagliari, Italy
Richard Porter,
University of Otago, New Zealand

***Correspondence:**
Lars Vedel Kessing
lars.vedel.kessing@regionh.dk

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *03 April 2018*
Accepted: *19 September 2018*
Published: *08 October 2018*

Citation:
Kessing LV and Miskowiak K (2018) Does Cognitive Dysfunction in Bipolar Disorder Qualify as a Diagnostic Intermediate Phenotype?—A Perspective Paper. Front. Psychiatry 9:490. doi: 10.3389/fpsyt.2018.00490

Cognitive dysfunction in bipolar disorder is a core illness symptom that has received intensive research interest over the past decade because of its negative impact on socio-occupational outcome, quality of life and illness prognosis (1–3). However, it is unclear whether patients' cognitive deficits comprise a diagnostic intermediate phenotype that may aid diagnostic accuracy and represent a key treatment target. The present perspective paper evaluates the present evidence and discusses whether cognitive dysfunction in bipolar disorder qualifies as a diagnostic intermediate phenotype using the Robin and Guze criteria of diagnostic validity (4) also concurrent with the later endophenotype concept (5) and extended criteria suggestions (6). The rationale for the Robin and Guze criteria was to develop criteria distinguishing between various psychiatric disorders and aiming for a valid psychiatric classification system (4). An intermediate phenotype was later defined as a measurable component along the pathway between disease and distal genotype, and have emerged as an important concept in the study of complex neuropsychiatric diseases (5). An endophenotype may be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature (5). The paper will review current data on cognitive dysfunction within (1) delineation of the clinical intermediate phenotype, (2) associations of the intermediate phenotype with para-clinical data such as brain imaging and blood-based data, (3) associations to family history / genetics, (4) characteristics during long-term

follow-up, and (5) treatment effects on cognition. Within each of these five points, the specificity of the findings in relation to bipolar disorder compared with schizophrenia and unipolar disorder will be summarized. The paper will identify knowledge gaps and suggest recommendations for future research within each of the five areas.

DELINEATION AND CHARACTERIZATION OF THE CLINICAL INTERMEDIATE PHENOTYPE

This area concerns whether cognitive dysfunction in bipolar disorder in remission is circumscribed clinically as a separate diagnostic intermediate phenotype of bipolar disorder and whether such an intermediate phenotype differs from similar intermediate phenotypes within related disorders such as schizophrenia and unipolar disorder.

Meta-analyses have consistently shown disturbances in executive function, verbal learning and memory, visual memory and attention in bipolar disorder compared with healthy control individuals (7–10). Cognitive impairment in the remitted phase of bipolar disorder is on average of a moderate effect size (7), however, with a substantial cognitive heterogeneity: 12–40% of patients present global cognitive impairments across several domains, 29–40% show selective deficits in attention and psychomotor speed, and 32–48% are relatively "cognitively intact" in comparison with norms (11). Subgroups with neurocognitive impairments present reduced functional capacity, more stress and poorer quality of life than patients who are cognitively intact, despite similar degrees of subsyndromal mood symptoms (2, 11, 12). Compared with bipolar disorder type II (hypomanic and depressive episodes; no manic episodes), bipolar disorder type I (manic and/or depressive episodes) seems to be associated with modestly more pronounced global cognitive impairment as well as increased disturbances in verbal memory, processing speed, executive function speed, and executive function accuracy (13).

On the other hand, cognitive deviances are not specific for bipolar disorder. Cognitive impairment is also prevalent in schizophrenia (14) and unipolar disorder (15), and there is no specific neuropsychological signature that can facilitate the diagnostic differentiation between bipolar disorder, schizophrenia, and unipolar disorder (16), notwithstanding, neuropsychological deficits appear more severe in schizophrenia (14, 17) and bipolar disorder (15). In schizophrenia and bipolar disorder, cognitive impairments have been found to correlate with socio-demographic (lower education and work capacity), clinical (more hospitalizations, longer duration of illness, negative psychotic symptoms, and non-remission status), treatment (antipsychotics, anti-cholinergics) variables and lower psychosocial functioning (1, 3, 18). Similar predictors of cognitive dysfunction are found in unipolar disorder but with more variable evidence, possibly because of the generally milder cognitive impairments in this patient group (19, 20).

Emotion dysregulation may be another cognitive feature of bipolar disorder that persists into periods of remission. Such deficits in "hot" (emotional) cognition are closely linked to emotional disturbances (21) and difficulties in socio-emotional behavior and interpersonal relations in bipolar disorder (22). Hot cognition abnormalities in bipolar disorder have been observed within three domains; emotional processing, reward processing, and emotion regulation [reviews in (23, 24)].

Emerging evidence points to partial persistence of such hot cognition dysfunction during remission in unipolar disorder, particularly within negative affect processing, (25) and the presence of similar abnormalities in healthy relatives of patients with unipolar disorder, at least at a neural level (25, 26). Hot cognition has not been systematically investigated across mood disorders and schizophrenia although some data point toward somewhat dissociable deficits in primary reward processing in unipolar disorder and schizophrenia (27). A key question remains whether deficits in experiencing rewards are independent of anhedonia in schizophrenia and whether level of observed reward disruption across unipolar disorder and schizophrenia a is a matter of severity rather than reflecting a qualitatively distinct mechanism (27). In contrast, a few studies of patients with bipolar disorder found evidence for a distinct positive bias in emotion processing and elevated reward responsiveness (28)—cognitive features that may in the future aid diagnostic discrimination between the disorders.

ASSOCIATIONS OF THE INTERMEDIATE PHENOTYPE WITH PARA-CLINICAL DATA SUCH AS BRAIN IMAGING AND BLOOD-BASED DATA

It is unknown whether shared manifestations of cognitive dysfunction across diagnostic categories also reflect shared neurobiological mechanisms or whether the sources of impairment differ. A recent study investigated the associations between general cognitive deficits (non-emotional or so called "cold") and functional network integrity measures including global and local efficiency of the whole brain, cingulo-opercular network (CON), frontoparietal network, and auditory network (29). Patients with schizophrenia and psychotic bipolar disorder had significantly reduced CON global efficiency compared with healthy controls (29). All patients with psychotic disorders had significantly reduced CON local efficiency, but the clinical groups did not differ from one another. The CON global efficiency was significantly associated with general cognitive ability across all groups and significantly mediated the association between psychotic disorder status and general cognition. It was concluded that these findings provide evidence that "reduced CON and subcortical network efficiency may play a role in the general cognitive deficit observed across the psychosis" (29).

Another common neural underpinning of cognitive deficits across bipolar disorder, unipolar disorder, and schizophrenia is aberrant task-related activity in the dorsal prefrontal cortex (PFC), although findings regarding the direction of the aberrant activity vary between studies with most evidence for *hypo*-activity in schizophrenia and bipolar disorder while the findings in unipolar disorder are more variable. In particular, we found

in a systematic review of >100 neuroimaging studies across bipolar disorder and unipolar disorder consistent evidence for abnormal (predominantly hypo-) activity in dorsal and lateral PFC cognitive control regions during performance on working memory, executive skills, memory encoding, and sustained attention (Miskowiak and Petersen, in press). Notably, the *direction* of this dorsal PFC activity depended on patients' performance levels. Dorsal PFC *hypo*-activity is consistently linked to impaired task performance; that is *reduced cognitive capacity*. In contrast, dorsal PFC *hyper*-activity is generally accompanied by normal performance levels and thus seems to reflect *reduced cortical efficiency*; that is, a need to recruit more neural resources to maintain normal performance. These associations are likely to explain the more consistent evidence for dorsal PFC hypo-activity in the generally more severely cognitively impaired patients groups (i.e., schizophrenia and bipolar disorder).

Another consistent finding in the review was reduced deactivation of the default mode network (DMN) and limbic structures during active task performance across bipolar disorder and unipolar disorder (ibid). This suggests that cognitive impairments across mood disorders are exacerbated by a failure to suppress task-irrelevant neural activity associated with emotional reactivity, self-focus and rumination (ibid).

Emerging neuroimaging evidence points to deficits in emotion dysregulation being a prominent feature of bipolar disorder, while unipolar disorder seems to be more consistently associated with negative processing biases (30). Emotion dysregulation in bipolar disorder seems associated with increased activity in limbic regions implicated in emotion-generation paired with deficient lateral prefrontal top-down control of emotional responses (31). However, this finding is not specific to bipolar disorder; indeed neuroimaging studies of social cognition in patients with mood disorders have generally revealed enhanced activation in limbic and emotion-related structures and attenuated activity within frontal regions associated with emotion regulation and higher cognitive functions. These results reveal an "overall lack of inhibition by higher-order cognitive structures on limbic and emotion-related structures during social cognitive processing in patients with mood disorders" (32). Critically, key variables, including illness burden, symptom severity, comorbidity, medication status, and cognitive load may moderate this pattern of neural activation (32).

Peripheral inflammation might be related to cognitive deficits in schizophrenia and bipolar disorder. Single studies suggest the role of C-reactive protein (CRP), interleukin (IL)-1 receptor antagonist, IL-6, and tumor necrosis factor-α (TNF-α) with its receptors in the development of cognitive impairment in bipolar disorder as summarized in reviews (33, 34). Due to low number of studies, it is difficult to draw conclusions on the involvement of CRP and cytokine alterations in the development of cognitive deficits in bipolar disorder. More consistent results indicate worse cognitive performance in schizophrenia patients with higher CRP levels (33). Evidence for the involvement of other cytokines in cognitive impairment in patients with schizophrenia is less convincing due to discordant results and scarcity of studies (33). Nevertheless, a larger study found that general cognitive abilities may be associated with IL-1Ra and sTNF-R1 in schizophrenia and with soluble CD40 ligand (sCD40L) and IL-1Ra in bipolar disorder patients (35).

ASSOCIATIONS TO FAMILY HISTORY / GENETICS

A recent meta-analysis of cognitive functions in first-degree relatives of probands with bipolar disorder and schizophrenia showed that probands with schizophrenia displayed cognitive deficits in all domains (d = 0.20–0.58) whereas probands with bipolar disorder underperformed healthy controls in processing speed, verbal fluency and speed based executive function tests (36). It was concluded that "inefficiency in processing information and impaired processing speed might be common vulnerability factors for major psychoses." On the other hand, "low performance in accuracy based tasks and deficits in general intellectual ability, verbal learning, planning, and working memory might be more specifically associated with risk for schizophrenia" (36). Further, we found in a systematic review of neuroimaging studies of healthy first-degree relatives of patients with bipolar disorder emerging evidence for abnormalities in emotional processing—and regulation and reward processing being candidate endophenotypes (37). We investigated this notion in a cohort of monozygotic twins at risk of either unipolar or bipolar disorder (reflected by a co-twin history of that disorder) (38). Interestingly, we found that twins at risk of bipolar disorder showed increased sensitivity and reactivity to positive social stimuli in comparison with individuals at risk of unipolar disorder and low-risk control twins. Together, these findings provide emerging evidence for positive bias being a putative neurocognitive endophenotype that is specific for bipolar disorder.

In terms of neurocognitive-genetic investigations, catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) are the two most studied candidate genes especially in patients with schizophrenia (39). Whereas BDNF Val66Met carriers seem to perform worse on verbal working memory, problem solving, and visuo-spatial abilities, COMT Val158Met carriers may perform better in working memory, attention, executive functioning with evidence of genotype by diagnosis interactions including high-risk individuals (39), although findings are not uniform (40, 41). In terms of genetic-structural MRI studies, "patients with schizophrenia are found to have reductions in the frontal, temporal, parietal cortices, and limbic regions, which are associated with BDNF, COMT, and neuregulin-1 (NRG1) genes" (39). Genetic-functional MRI studies in bipolar disorder are sparse and results conflicting (39, 42).

CHARACTERISTICS OF COGNITION DURING LONG-TERM FOLLOW-UP

Cognitive deficits in bipolar disorder in remission seem to persist over time or even progress supporting the view that these deficits qualify for an intermediary phenotype. Using

a 5 years longitudinal cohort, 91 individuals with bipolar disorder and 17 healthy controls were administered a battery of neuropsychological tests that captured four main areas of executive functioning that were found to persist over time (43).

Based on cross-sectional studies, cognitive deficits seem to deteriorate during late stages of the disorder (44). In contrast, there is a lack of longitudinal studies on cognition in bipolar disorder (45, 46) with the largest study being the study by Ryan et al. (43, 47). A new meta-analysis comparing short-term (mean of 1.5 years) and long-term (mean of 5.5 years) neurocognitive changes in 643 euthymic patients with bipolar disorder, 367 healthy controls and 168 patients with schizophrenia found no cognitive changes over time in any of the three cohorts (46). Besides the small sample sizes in each study, limitations included short follow-up (mean follow-up period of 4.6 years) specifically for studies of bipolar disorder, high attrition rates (up to 45%) among all participants and strict euthymia criteria for bipolar patients included in the analyses, which may have introduced a selection bias (including only the high functioning patients), as also concluded in a prior similar meta-analysis of bipolar disorder (48).

Regarding cognitive functioning in unipolar disorder, some cross-sectional studies suggest that cognitive function in the euthymic phase is associated with the duration or number of prior episodes [(49–54), for a review see: (19)].

Studies on the risk of developing dementia in unipolar disorder and bipolar disorder have recently been summarized (55). It was concluded that a meta-analysis including 44 studies on depression and six on bipolar disorder (56) as well as *all* subsequent studies have confirmed that unipolar disorder (56–60) and bipolar disorder (56–58, 60, 61) are associated with increased risks of developing dementia long-term (as a clinical diagnosis). It was further concluded that longitudinal studies of bipolar disorder may have had to short follow-up time (mean follow-up period of 4.62 years) to reveal a decrease in *neuropsychological* functioning over time in contrast to the much longer follow-up time in studies with dementia as the outcome measure (55).

TREATMENT EFFECTS ON COGNITION

A recent systematic review on novel pharmacological (N-acetyl cysteine, pregnolone, ketamine and pramipexole, mifepristone, galantamine, insulin, erytrophoietin, withania somnifera, and citicoline) and psychological treatments (cognitive remediation and cognitive training) on cognition in bipolar disorder identified 19 studies of which 13 were RCTs and six were open-label or non-randomized studies (62). The efficacy on cognition was overall disappointing or preliminary, possibly due to several methodological challenges. Similarly, a later controlled trial found no effect of methylene blue on cognition in bipolar disorder (63). Among the most promising pharmacological treatments for cognitive dysfunction across bipolar disorder and unipolar disorder is erythropoietin, but the evidence is still preliminary (62, 64). These findings are partly in accordance with findings within unipolar disorder and schizophrenia with only a few studies have shown benefit for pharmacological treatments (64–66) and with a lack of successful replication of these data (64, 66, 67). However, psychological treatment programs involving intensive cognitive remediation have revealed more consistent positive effects on cognition in schizophrenia (68, 69) and emerging evidence in mood disorders (64, 70).

CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

It is clear from the present summary of studies on cognition in bipolar disorder that at the current state of knowledge cognition in bipolar disorder does not qualify as a diagnostic intermediate phenotype using the Robin and Guze criteria of diagnostic validity (4) or the later endophenotype concept (5, 6), although emerging evidence points to hot cognition abnormalities representing promising putative endophenotypes. Rather, extant findings within four of the five Robin and Guze criteria generally support the dimensional hypothesis that a shared neurobiological mechanism underlies cognitive impairment across bipolar disorder, unipolar disorder and schizophrenia: (1) there may not be a specific neuropsychological signature that differentiate cognitive deviances in bipolar disorder from those in schizophrenia and unipolar disorder (only potentially within hot cognition); (2) brain imaging or blood-based data does not at the current state of knowledge differentiate between cognitive dysfunction in bipolar disorder, schizophrenia or unipolar disorder; (3) probands to patients with bipolar disorder, schizophrenia, and unipolar disorder show similar cognitive deficits although with varying severity, except for within hot cognition. Investigations of genetic associations to cognitive deviances are in its early stages, only (4) treatment effects of pharmacological or psychological interventions on cognition do not seem to differ within bipolar disorder, schizophrenia and unipolar disorder. The fourth Robin and Guze criterion seems fulfilled as cognitive deficits in bipolar disorder seem either stable over time or progress during long-term supporting cognitive deficits as an intermediary phenotype.

It is further evident from the present summary of studies on cognition in bipolar disorder that a number of research initiatives are needed within all five of the Robin and Guze criteria.

1. Research is needed integrating "hot" and "cold" cognition in bipolar disorder. Few if any studies have investigated how emotion dysregulation (i.e., hot cognition) interact with cold cognition. As recently emphasized, cognitive biases, reward processing and motivation, rumination, and mood stability may play significant roles in the manner in which attention, appraisal, and response processes are deployed in mood disorders (71).

2. Emotion dysregulation (hot cognition) should be investigated across mood disorders and schizophrenia. Emotion dysregulation has emerged as a new research area that may characterize mood disorders, and potentially specifically bipolar disorder, rather than schizophrenia. Although these speculations are clinically plausible, emotion dysregulation has not been systematically investigated across mood disorders and schizophrenia.

3. Structural and functional neuroimaging data on cognitive features ("cold" and "hot") should be integrated across mood disorders. Such multimodal neuroimaging studies aiming to identify structure-function relationships in neural circuitry have previously been suggested in relation to bipolar disorder in general (24). As highlighted, a very small number of studies examined structure-function relationships in prefrontal cortical-amygdala circuitry in adults with bipolar disorder type I and bipolar disorder type II (24). We suggest integrating investigations of "cold" and "hot" cognitive features into the loop and across mood disorders.

4. Neurogenetics should be integrated into research in cognitive disturbances in patients with mood disorders and schizophrenia and in their first degree relatives.

5. Research in cognitive enhancement treatments. We have previously suggested implementation of a 'neurocircuitry-based' biomarker model to evaluate neural target engagement in cognitive enhancement (62). We suggest that a valid biomarker model for cognitive improvement must fulfill five key validity criteria: it must (i) be sensitive to a treatment with pro-cognitive effects, (ii) produce similar effects in patients with cognitive dysfunction and healthy participants, (iii) be sensitive to effective treatments with different neurochemical mechanisms, (iv) be unresponsive to ineffective treatments, and (v) be sensitive to both cognitive improvement and—decline. A potential solution to the problem is a step-wise approach with which we: (i) identify the most reliable functional neuronal correlates of cognitive deficits in neuropsychiatric disorders, (ii) select one of the most promising candidate treatments and test its ability to modulate the activity in these dysfunctional neural circuitries in a short-term proof-of-concept fMRI study, and (iii) if target engagement is shown in (ii), then test the effects of this candidate treatment in a longer-term clinical phase 2 trial in patients using fMRI to elucidate the neuronal changes underlying potential pro-cognitive effects.

More evidence is needed confirming whether cognitive deficits comprise a diagnostic intermediate phenotype in bipolar disorder. The long-term perspective is that cognitive deficits may aid diagnostic accuracy and represent a key treatment target in bipolar disorder.

AUTHOR CONTRIBUTIONS

LK developed the idea and drafted the first version of the paper. KM revised the paper and both authors accepted the final version of the paper.

REFERENCES

1. Tse S, Chan S, Ng KL, Yatham LN. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. *Bipolar Disord.* (2014) 16:217–29. doi: 10.1111/bdi.12148
2. Jensen JH, Knorr U, Vinberg M, Kessing LV, Miskowiak KW. Discrete neurocognitive subgroups in fully or partially remitted bipolar disorder: Associations with functional abilities. *J Affect Disord.* (2016) 205:378–86. doi: 10.1016/j.jad.2016.08.018
3. Jaeger J, Berns S, Loftus S, Gonzalez C, Czobor P. Neurocognitive test performance predicts functional recovery from acute exacerbation leading to hospitalization in bipolar disorder. *Bipolar Disord.* (2007) 9:93–102. doi: 10.1111/j.1399-5618.2007.00427.x
4. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry* (1970) 126:983–87.
5. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* (2003) 160:636–45. doi: 10.1176/appi.ajp.160.4.636
6. Kendler KS, Neale MC. Endophenotype: a conceptual analysis. *Mol Psychiatry* (2010) 15:789–97. doi: 10.1038/mp.2010.8
7. Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JT, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr Scand.* (2013) 128(3):149-162. doi: 10.1111/acps.12133
8. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr Scand Suppl.* (2007) 434:17–26. doi: 10.1111/j.1600-0447.2007.01055.x
9. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J Affect Disord.* (2009) 113:1–20. doi: 10.1016/j.jad.2008.06.009
10. Mann-Wrobel MC, Carreno JT, Dickinson D. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disord.* (2011) 13:334–42. doi: 10.1111/j.1399-5618.2011.00935.x
11. Miskowiak KW, Burdick KE, Martinez-Aran A, Bonnin CM, Bowie CR, Carvalho AF, et al. Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. *Bipolar Disord.* (2018) 20:184–94. doi: 10.1111/bdi.12595
12. Sole B, Jimenez E, Torrent C, Del Mar Bonnin C, Torres I, Reinares M, et al. Cognitive variability in bipolar II disorder: who is cognitively impaired and who is preserved. *Bipolar Disord.* (2016) 18:288–99. doi: 10.1111/bdi.12385
13. Bora E. Neurocognitive features in clinical subgroups of bipolar disorder: a meta-analysis. *J Affect Disord.* (2018) 229:125–34. doi: 10.1016/j.jad.2017.12.057
14. Bortolato B, Miskowiak KW, Kohler CA, Vieta E, Carvalho AF. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat.* (2015) 11:3111–25. doi: 10.2147/NDT.S76700
15. Porter RJ, Robinson LJ, Malhi GS, Gallagher P. The neurocognitive profile of mood disorders - a review of the evidence and methodological issues. *Bipolar Disord.* (2015) 17 (Suppl 2):21–40. doi: 10.1111/bdi.12342
16. Szmulewicz AG, Valerio MP, Smith JM, Samame C, Martino DJ, Strejilevich SA. Neuropsychological profiles of major depressive disorder and bipolar disorder during euthymia. a systematic literature review of comparative studies. *Psychiatry Res.* (2017) 248:127–33. doi: 10.1016/j.psychres.2016.12.031
17. Van Rheenen TE, Lewandowski KE, Tan EJ, Ospina LH, Ongur D, Neill E, et al. Characterizing cognitive heterogeneity on the schizophrenia-bipolar disorder spectrum. *Psychol Med.* (2017) 47:1848–64. doi: 10.1017/S0033291717000307
18. Kuswanto C, Chin R, Sum MY, Sengupta S, Fagiolini A, McIntyre RS, et al. Shared and divergent neurocognitive impairments in adult patients with schizophrenia and bipolar disorder: whither the evidence? *Neurosci Biobehav Rev.* (2016) 61:66–89. doi: 10.1016/j.neubiorev.2015.12.002
19. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect. Disord.* (2011) 134:20–31. doi: 10.1016/j.jad.2010.11.011

20. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res.* (2006) 145:39–48. doi: 10.1016/j.psychres.2005.11.011
21. Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology* (2004) 29:1734–40. doi: 10.1038/sj.npp.1300492
22. Kerr N, Dunbar RI, Bentall RP. Theory of mind deficits in bipolar affective disorder. *J Affect. Disord.* (2003) 73:253–9. doi: 10.1016/S0165-0327(02)00008-3
23. Wessa M, Linke J. Emotional processing in bipolar disorder: behavioural and neuroimaging findings. *Int. Rev Psychiatry* (2009) 21:357–67. doi: 10.1080/09540260902962156
24. Phillips ML, Swartz HA. A critical appraisal of neuroimaging studies of bipolar disorder: toward a new conceptualization of underlying neural circuitry and a road map for future research. *Am J Psychiatry* (2014) 171:829–43. doi: 10.1176/appi.ajp.2014
25. Miskowiak KW, Carvalho AF. 'Hot' cognition in major depressive disorder: a systematic review. *CNS Neurol Disord Drug Targets* (2014) 13:1787–803.
26. Miskowiak K, Glerup L, Vestbo C, Harmer CJ, Reinecke A, Macoveanu J, et al. Different neural and cognitive response to emotional faces in healthy monozygotic twins at risk of depression. *Psychol Med.* (2015) 45:1447–58. doi: 10.1017/S0033291714002542
27. Anticevic A, Schleifer C, Youngsun TC. Emotional and cognitive dysregulation in schizophrenia and depression: understanding common and distinct behavioral and neural mechanisms. *Dialogues Clin Neurosci.* (2015) 17:421–34.
28. de Brito Ferreira Fernandes F, Gigante AD, Berutti M, Amaral JA, de Almeida KM, de Almeida Rocca CC, et al. Facial emotion recognition in euthymic patients with bipolar disorder and their unaffected first-degree relatives. *Compr Psychiatry* (2016) 68:18–23. doi: 10.1016/j.comppsych.2016.03.001
29. Sheffield JM, Kandala S, Tamminga CA, Pearlson GD, Keshavan MS, Sweeney JA, et al. Transdiagnostic associations between functional brain network integrity and cognition. *JAMA Psychiatry* (2017) 74:605–13. doi: 10.1001/jamapsychiatry.2017.0669
30. Miskowiak KW, Carvalho AF. 'Hot' cognition in major depressive disorder: a systematic review. *CNS Neurol Disord Drug Targets* (2014) 13:1787–803.
31. Townsend JD, Torrisi SJ, Lieberman MD, Sugar CA, Bookheimer SY, Altshuler LL. Frontal-amygdala connectivity alterations during emotion downregulation in bipolar I disorder. *Biol Psychiatry* (2013) 73:127–35. doi: 10.1016/j.biopsych.2012.06.030
32. Cusi AM, Nazarov A, Holshausen K, Macqueen GM, McKinnon MC. Systematic review of the neural basis of social cognition in patients with mood disorders. *J Psychiatry Neurosci.* (2012) 37:154–69. doi: 10.1503/jpn.100179
33. Misiak B, Stanczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: a systematic review. *Schizophr Res.* (2018) 192:16–29. doi: 10.1016/j.schres.2017.04.015
34. Rosenblat JD, Brietzke E, Mansur RB, Maruschak NA, Lee Y, McIntyre RS. Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: evidence, pathophysiology and treatment implications. *J Affect Disord.* (2015) 188:149–59. doi: 10.1016/j.jad.2015.08.058
35. Hope S, Hoseth E, Dieset I, Morch RH, Aas M, Aukrust P, et al. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. *Schizophr Res.* (2015) 165:188–94. doi: 10.1016/j.schres.2015.04.004
36. Bora E. A comparative meta-analysis of neurocognition in first-degree relatives of patients with schizophrenia and bipolar disorder. *Eur Psychiatry* (2017) 45:121–8. doi: 10.1016/j.eurpsy.2017.06.003
37. Miskowiak KW, Kjaerstad HL, Meluken I, Petersen JZ, Maciel BR, Kohler CA, et al. The search for neuroimaging and cognitive endophenotypes: a critical systematic review of studies involving unaffected first-degree relatives of individuals with bipolar disorder. *Neurosci Biobehav Rev.* (2017) 73:1–22. doi: 10.1016/j.neubiorev.2016.12.011
38. Kaersgaard S, Meluken I, Kessing LV, Vinberg M, Miskowiak KW. Increased sensitivity to positive social stimuli in monozygotic twins at risk of bipolar vs. unipolar disorder. *J Affect Disord.* (2018) 232:212–18. doi: 10.1016/j.jad.2018.02.055
39. Kurnianingsih YA, Kuswanto CN, McIntyre RS, Qiu A, Ho BC, Sim K. Neurocognitive-genetic and neuroimaging-genetic research paradigms in schizophrenia and bipolar disorder. *J Neural Transm.* (2011) 118:1621–39. doi: 10.1007/s00702-011-0672-z
40. Burdick KE, Funke B, Goldberg JF, Bates JA, Jaeger J, Kucherlapati R, et al. COMT genotype increases risk for bipolar I disorder and influences neurocognitive performance. *Bipolar Disord.* (2007) 9:370–6. doi: 10.1111/j.1399-5618.2007.00384.x
41. Tramontina JF, Yates D, Magalhaes PV, Trentini C, Sant'anna MK, Fries GR, et al. Brain-derived neurotrophic factor gene val66met polymorphism and executive functioning in patients with bipolar disorder. *Rev Bras Psiquiatr.* (2009) 31:136–40. doi: 10.1590/S1516-44462009000200010
42. Miskowiak KW, Kjaerstad HL, Stottrup MM, Svendsen AM, Demant KM, Hoeffding LK, et al. The catechol-O-methyltransferase (COMT) Val158Met genotype modulates working memory-related dorsolateral prefrontal response and performance in bipolar disorder. *Bipolar Disord.* (2017) 19:214–24. doi: 10.1111/bdi.12497
43. Ryan KA, Assari S, Pester BD, Hinrichs K, Angers K, Baker A, et al. Similar trajectory of executive functioning performance over 5 years among individuals with bipolar disorder and unaffected controls using latent growth modeling. *J Affect Disord.* (2016) 199:87–94. doi: 10.1016/j.jad.2016.04.016
44. Rosa AR, Magalhaes PV, Czepielewski L, Sulzbach MV, Goi PD, Vieta E, et al. Clinical staging in bipolar disorder: focus on cognition and functioning. *J Clin Psychiatry* (2014) 75:e450–6. doi: 10.4088/JCP.13m08625
45. Mora E, Portella MJ, Forcada I, Vieta E, Mur M. Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychol Med.* (2013) 43:1187–96. doi: 10.1017/S0033291712001948
46. Bora E, Ozerdem A. Meta-analysis of longitudinal studies of cognition in bipolar disorder: comparison with healthy controls and schizophrenia. *Psychol Med.* (2017) 47:2753–66. doi: 10.1017/S0033291717001490
47. Ryan KA, Assari S, Angers K, Marshall DF, Hinrichs K, Easter R, et al. Equivalent linear change in cognition between individuals with bipolar disorder and healthy controls over 5 years. *Bipolar Disord.* (2017) 19:689–97. doi: 10.1111/bdi.12532
48. Samame C, Martino DJ, Strejilevich SA. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. *J Affect Disord.* (2014) 164:130–8. doi: 10.1016/j.jad.2014.04.028
49. Kessing LV, Dam H, Joergensen OS, Bolwig TG. Cognitive impairment in affective disorders. Relation to illness characteristics. *Nord J Psychiatry* (1996) 50:305–16.
50. Kessing LV. Cognitive impairment in the euthymic phase of affective disorder. *Psychol. Med.* (1998) 28:1027–38.
51. Hasselbalch BJ, Knorr U, Hasselbalch SG, Gade A, Kessing LV. The cumulative load of depressive illness is associated with cognitive function in the remitted state of unipolar depressive disorder. *Eur Psychiatry* (2013) 28:349–55. doi: 10.1016/j.eurpsy.2012.03.004
52. Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med.* (1996) 26:591–603. doi: 10.1017/S0033291700035662
53. Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. *J Affect Disord.* (2005) 89:125–35. doi: 10.1016/j.jad.2005.09.006
54. Bhardwaj A, Wilkinson P, Srivastava C, Sharma M. Cognitive deficits in euthymic patients with recurrent depression. *J Nerv Ment Dis.* (2010) 198:513–5. doi: 10.1097/NMD.0b013e3181e4c5ba
55. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatr Scand.* (2017) 135:51–64. doi: 10.1111/acps.12667
56. da SJ, Goncalves-Pereira M, Xavier M, Mukaetova-Ladinska EB. Affective disorders and risk of developing dementia: systematic review. *Br J Psychiatry* (2013) 202:177–86. doi: 10.1192/bjp.bp.111.101931
57. Kessing LV, Olsen EW, Mortensen PB, Andersen PK. Dementia in affective disorder: a case-register study. *Acta Psychiatr Scand.* (1999) 100:176–85.
58. Kessing LV, Nilsson FM. Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. *J Affect Disord.* (2003) 73:261–9. doi: 10.1016/S0165-0327(02)00004-6

59. Kessing LV. Depression and the risk for dementia. *Curr Opin Psychiatry* (2012) 25:457–61. doi: 10.1097/YCO.0b013e328356c368
60. Chen MH, Li CT, Tsai CF, Lin WC, Chang WH, Chen TJ, et al. Risk of subsequent dementia among patients with bipolar disorder or major depression: a nationwide longitudinal study in Taiwan. *J Am Med Dir Assoc.* (2015) 16:504–8. doi: 10.1016/j.jamda.2015.01.084
61. Wu KY, Chang CM, Liang HY, Wu CS, Chia-Hsuan WE, Chen CH, et al. Increased risk of developing dementia in patients with bipolar disorder: a nested matched case-control study. *Bipolar Disord.* (2013) 15:787–94. doi: 10.1111/bdi.12116
62. Miskowiak KW, Carvalho AF, Vieta E, Kessing LV. Cognitive enhancement treatments for bipolar disorder: a systematic review and methodological recommendations. *Eur Neuropsychopharmacol.* (2016) 26:1541–61. doi: 10.1016/j.euroneuro.2016.08.011
63. Alda M, McKinnon M, Blagdon R, Garnham J, MacLellan S, O'Donovan C, et al. Methylene blue treatment for residual symptoms of bipolar disorder: randomised crossover study. *Br J Psychiatry* (2017) 210:54–60. doi: 10.1192/bjp.bp.115.173930
64. Miskowiak KW, Ott CV, Petersen JZ, Kessing LV. Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. *Eur Neuropsychopharmacol.* (2016) 26:1845–67. doi: 10.1016/j.euroneuro.2016.09.641
65. Harvey PD, Bowie CR. Cognitive enhancement in schizophrenia: pharmacological and cognitive remediation approaches. *Psychiatr Clin North Am.* (2012) 35:683–98. doi: 10.1016/j.psc.2012.06.008
66. Harvey PD, Sand M. Pharmacological augmentation of psychosocial and remediation training efforts in schizophrenia. *Front Psychiatry* (2017) 8:177. doi: 10.3389/fpsyt.2017.00177
67. Keefe RS, Davis VG, Spagnola NB, Hilt D, Dgetluck N, Ruse S, et al. Reliability, validity and treatment sensitivity of the Schizophrenia Cognition Rating Scale. *Eur Neuropsychopharmacol.* (2015) 25:176–84. doi: 10.1016/j.euroneuro.2014.06.009
68. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry* (2011) 168:472–85. doi: 10.1176/appi.ajp.2010.10060855
69. Revell ER, Neill JC, Harte M, Khan Z, Drake RJ. A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophr Res.* (2015) 168:213–22. doi: 10.1016/j.schres.2015.08.017
70. Lewandowski KE, Sperry SH, Cohen BM, Norris LA, Fitzmaurice GM, Ongur D, et al. Treatment to Enhance Cognition in Bipolar Disorder (TREC-BD): efficacy of a randomized controlled trial of cognitive remediation versus active control. *J Clin Psychiatry* (2017) 78:e1242–9. doi: 10.4088/JCP.17m11476
71. Malhi GS, Byrow Y, Fritz K, Das P, Baune BT, Porter RJ, et al. Mood disorders: neurocognitive models. *Bipolar Disord.* (2015) 17 (Suppl. 2):3–20. doi: 10.1111/bdi.12353

Conflict of Interest Statement: LK has received consultancy fees from Sunovion in the past 3 years. KM has received consultancy fees from Lundbeck and Allergan in the past 3 years.

frontiers in Psychiatry

MINI REVIEW
published: 11 October 2018
doi: 10.3389/fpsyt.2018.00493

Assessment and Management of Cognitive and Psychosocial Dysfunctions in Patients With Major Depressive Disorder: A Clinical Review

Andrea Fiorillo[1], Bernardo Carpiniello[2], Serafino De Giorgi[3], Silvestro La Pia[4], Giuseppe Maina[5], Gaia Sampogna[1], Edoardo Spina[6], Alfonso Tortorella[7] and Antonio Vita[8,9]*

[1] Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy, [2] Department of Public Health, Clinical and Molecular Medicine, University of Cagliari, Cagliari, Italy, [3] Department of Mental Health, ASL Lecce, Lecce, Italy, [4] Department of Mental Health, ASL Napoli 3 Sud, Naples, Italy, [5] AOU San Luigi Gonzaga, University of Turin, Turin, Italy, [6] Department of Clinical and Experimental Pharmacology, University of Messina, Messina, Italy, [7] Department of Psychiatry, University of Perugia, Perugia, Italy, [8] Neuroscience Section, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [9] Department of Mental Health, Spedali Civili Hospital, Brescia, Italy

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Nefize Yalin,
King's College London,
United Kingdom
Giuseppe Carrà,
Università degli studi di Milano Bicocca, Italy

***Correspondence:**
Andrea Fiorillo
andrea.fiorillo@unicampania.it

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *19 April 2018*
Accepted: *20 September 2018*
Published: *11 October 2018*

Citation:
Fiorillo A, Carpiniello B, De Giorgi S, La Pia S, Maina G, Sampogna G, Spina E, Tortorella A and Vita A (2018) Assessment and Management of Cognitive and Psychosocial Dysfunctions in Patients With Major Depressive Disorder: A Clinical Review. Front. Psychiatry 9:493. doi: 10.3389/fpsyt.2018.00493

Background: Full functional recovery is defined as a state in which patients are again able to enjoy their usual activities, return to work, and take care of themselves, and it should represent the end goal of treatment in patients with major depressive disorder (MDD). Patients with MDD report many unmet needs, including residual cognitive symptoms, lack of improvement in psychosocial functioning and life satisfaction, even during mood symptom remission. In this paper, we aim to: (a) identify the available assessment tools for evaluating cognitive and psychosocial functioning in patients with MDD; (b) provide an overview of therapeutic options that can improve full functional recovery in MDD also by improving cognitive symptoms.

Methods: The relevant databases MEDLINE, ISI Web of Knowledge—Web of Science Index, Cochrane Reviews Library and PsychoINFO were searched for identifying papers on validated tools for the assessment of cognitive and personal functioning in patients with MDD.

Results: New assessment tools (such as the THINC-it TOOL, the COBRA, the SCIP-D, and the UPSA-D) have been developed for evaluating the cognitive dysfunction in MDD patients. Adopting these tools in the clinical routine practice is useful to evaluate the improvement in cognitive functioning and, therefore, the achievement of full functioning recovery. The optimal management of patients with MDD include the combination of pharmacological compounds and psychosocial interventions for achieving full functional recovery in patients with MDD.

Conclusions: Full functional recovery must be the target of any treatment programme for patients with MDD. In order to achieve this goal, it is necessary to develop personalized treatment and integrate psychosocial and psychopharmacological interventions.

Keywords: assessment tools, cognitive symptoms, full functional recovery, major depressive disorder, personal functioning

INTRODUCTION

Depression is a complex disorder with multiple symptomatological clusters, including emotional, cognitive, and physical symptoms (1). From 2005, a significant increase in the incidence of the disorder of almost 20% has been observed (2). In 2015, depressive disorders were the greatest contributor to non-fatal health loss (2, 3). The average lifetime prevalence of major depressive disorder (MDD) is estimated at 14.6% in high-income countries (4). Moreover, MDD represents the leading cause of disability burden worldwide (5), accounting for 2.5% of global Disability Adjusted Life Years lost (6), especially in women (2).

While in the past remission was considered the only clinical endpoint in the management of patients with MDD (7), more recently the concept of full functional recovery has been proposed as the ultimate therapeutic objective (8, 9). In fact, it is now clear that many patients with MDD who achieve symptomatic remission do not report a substantial improvement in psychosocial functioning and satisfaction with life (10, 11). Full functional recovery can be defined as a condition in which the patient starts to enjoy his/her usual activities again, returns to work and is able to take care of him/herself (12, 13). The achievement of full functional recovery in patients with MDD may be hampered by patient and illness-related factors. The former includes age, pre-morbid level of functioning, level of education, work condition, comorbidity with other psychiatric diseases, and other medical conditions. The illness-related factors include the severity of clinical episodes, the effectiveness of treatments, time to remission, maintenance and quality of remission (13–17).

The main unmet need in the treatment of patients with MDD, who have responded to classic antidepressants, is the presence of residual symptoms, such as lack of energy, concentration problems, and sleep disturbances (12). Cognitive symptoms (namely deficits in attention, memory, executive function, and processing speed) (18), which have been neglected for many years in the clinical management of mood disorders, may represent the link between symptomatic remission and functional recovery (19). Neurocognition is a core feature of depressive episodes; cognitive symptoms can limit patients' psychosocial functioning, and achieving "cognitive remission" has been claimed as a relevant goal in the treatment of MDD (20).

Although a good antidepressant therapy should not only aim to improve affective symptoms, but also cognitive symptoms, psychosocial functioning, work functioning, and quality of life (21), the majority of clinical studies on MDD evaluate the effectiveness of treatments on affective symptoms only (19). In fact, among the most frequently used tools to assess outcomes from MDD, only three of the top 20 explore functional domains, and these have been used in <5% of trials with patients with depression (14). Moreover, different tools are available for evaluating these dimensions, being different in structure, content, length, way of compilation and target population. In this manuscript, we aim to perform a clinical review on the recent assessment tools for evaluating cognitive and psychosocial functioning in patients with MDD. Finally, a critical insight on the translation from the evaluation to the appropriate treatment of cognitive symptoms is provided.

Abbreviations: COBRA, cognitive complaints in bipolar disorder rating assessment; MoCA, montreal cognitive assessment; MDD, major depressive disorder; Q-LES-Q, quality of life enjoyment and satisfaction questionnaire; RI, recovery index; SCIP-D, screen for cognitive impairment in psychiatry-depression; UPSA, university of california san diego performance-based skills assessment; WSAS, work and social adjustment scale.

MATERIALS AND METHODS

Search Strategy

The relevant databases MEDLINE, ISI Web of Knowledge—Web of Science Index, Cochrane Reviews Library and PsychoINFO were searched for papers published in the last 5 years. Previous years had already been covered by Bortolato et al. (22) (for assessment tools evaluating cognitive functioning in patients with MDD) and by Lam et al. (14) (for assessment tools evaluating psychosocial functioning in patients with MDD) and we aim to update their data with findings from more recent trials.

The key words "depressive disorder," "major depressive disorder," "depressed mood" matched with "cognitive symptoms," "cognitive functioning," "cognitive deficits," "psychosocial functioning," "work functioning," "social functioning," and "assessment tools" were entered in the relevant databases. Only papers written in English and published in peer-reviewed journals were included in our review.

The reference lists of all papers selected in the primary search were manually searched for other potential manuscripts. Recently published international guidelines on the management of patients with MDD were also searched. The results of the search were independently evaluated by two authors who have analyzed all relevant papers.

RESULTS

In the last years, new assessment tools have been developed for evaluating the cognitive dysfunction in MDD patients. In particular, in 2017 Harvey et al. (23) tested the psychometric validity of the "University of California San Diego Performance-based Skills assessment (UPSA)" in patients with MDD, bipolar disorder, mild cognitive impairment, Alzheimer's disease and healthy older adults. The UPSA has been originally developed to assess older, community-dwelling patients with schizophrenia or severe mental illness and it has been adapted to assess functional capacity in patients with MDD (23). Authors found that UPSA can provide clinically relevant information for the management of patients with MDD, since it measures the everyday functioning skills in different function domains. In fact, the UPSA composite score correlates with cognitive performance in the real-world of persons with MDD but it is not influenced from the clinical mood symptoms of depression (23).

In 2016, McIntyre et al. developed the THINC-it TOOL (24–26) which is available as an application for smartphones, tablets, and PC. It can be used to specifically assess the level of cognitive dysfunction in patients with depressive disorders. This tool requires ∼10–15 min to be completed (25), and therefore

can be easily implemented in clinical practice. Cognitive deficits measured by the THINC-it tool are associated with significant psychosocial impairment in MDD (27).

The Montreal Cognitive Assessment (MoCA) is a brief screening tool originally developed for assessing the most common neurocognitive deficits in patients with mild cognitive impairment (28). Recently, it has been tested in a sample of patients with MDD, showing a valid and reliable proprieties with good internal consistency.

When assessing cognitive symptoms, it is essential to differentiate between objective and subjective cognitive deficits (such as memory or concentration complaints), since the correct identification of objective dysfunctions is necessary for monitoring the effects of pharmacological and non-pharmacological treatments. To this end, two new assessment tools have been validated recently, the Screen for Cognitive Impairment in Psychiatry-Depression (SCIP-D) and the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) (29). In particular, the SCIP requires <20 min to be completed and assesses verbal learning, working memory, verbal fluency, delayed memory and processing speed; while COBRA evaluates the subjective dimensions of cognitive complaints. These two instruments, originally developed for patients with bipolar disorders, have shown good psychometric properties and can be easily administered to patients with MDD.

Among the instruments for the evaluation of social functioning in patients with MDD, extensively reported by Lam et al. (14), it has been recently developed the "Recovery Index" (RI) (30). This instrument is based on the combination of the WSAS and Q-LES-Q scales, and it provides information on social, personal, and work functioning (30). The index can be easily calculated by accessing a web platform and entering the mean scores obtained by the patient at the WSAS and at the Q-LES-Q. In particular, a higher score at the RI means a higher level of functional recovery. This index has good psychometric properties, it is easy to use, and can be adopted in clinical and research settings. The details of all instruments are reported in **Table 1**.

DISCUSSION

Although the paradigm of early diagnosis and individualized treatment represents the mainstay of the optimal management of patients with MDD (12), several unmet needs still exist and are reported by patients. In particular, cognitive dysfunctions represent a key determinant of functional disability in MDD patients (8, 31, 32) which can persist beyond clinical symptom remission (32), limiting work functioning, and contributing to the overall disability associated with MDD (22, 24, 33–38). It has been extensively reported that not paying attention to the cognitive dimension in patients with MDD may hamper the achievement of full recovery. For many years, cognition has been mainly evaluated in patients with other severe mental disorders, such as schizophrenia or bipolar disorders, and has not been considered a core dimension of the clinical presentation of patients with MDD. Nowadays, the establishment of the full functional recovery as new endpoint in the treatment of patients with MDD has highlighted the need to assess adequately cognitive symptoms and then, treat them.

The main finding of this clinical review is that several assessment tools exist for evaluating functional capacity. In particular, the UPSA has been useful to evaluate the everyday living skills, which is often a neglected aspect of other assessment tools (23). The UPSA gave the opportunity to evaluate the functional capacity, independently from mood symptoms. However, the UPSA has been developed in a pre-digital era and therefore its use may be overcome by modern technology. Therefore, other assessment instruments have been recently developed by including digital skills in the use of smartphones or devices, whose use has become widespread.

As regards the assessment of cognitive functioning, SCIP-D and COBRA are two new assessment tools recently validated in patients with MDD. In particular, the SCIP-D is very short and easy to use and therefore may be routinely administered in clinical practice; however, this instrument does not provide a full examination of neurocognitive functioning and it is better considered as a screening tool (39). The COBRA has a lower level of sensitivity and specificity compared to the SCIP-D for assessing objective cognitive dysfunctions; some authors have used a combined version of the two scales improving their validity (29).

The THINC-it TOOL (26) is a free-of-charge, digitalized, downloadable, application available for tablets and smartphones, which can be used in several clinical settings. Moreover, it is user-friendly and can be self-administered so that patients can regularly check their improvement in cognitive functioning. However, the need to be skilled in the use of smartphones or PCs may be a limitation, particularly in older patients. The MoCA is a reliable and valid instrument for measuring cognitive impairment in MDD patients. This instrument, which has already been translated in several languages, is quite short and requires lower time for completion compared to a complete set of neurocognitive tests. Both the MoCA and the SCIP-D (29) can be considered good screening tools for the evaluation of cognitive functioning.

The availability of instruments for the assessment of all the dimensions of cognitive functioning is probably a first step toward the shift in clinical practice from symptom remission to full functional recovery. In order to increase feasibility in routine care, these assessment tools should be easy to use and not time-consuming, as is the case with the Think-it tool or the SCIP-D. Also the "Recovery Index" may be implemented in routine care for the evaluation of psychosocial functioning of patients with MDD given its usefulness and easiness to use.

By assessing the cognitive functioning of patients with MDD, the positive impact of some pharmacological agents on these domains becomes clear. In the vast majority of patients, the treatment of cognitive symptoms represents a relevant problem in clinical practice, which impacts on the level of personal and cognitive functioning of patients. The use of tools focused on cognitive functioning or of tools with a mixed focus on social and cognitive functioning, such as the "Recovery Index," should be promoted in clinical practice, considering the central role

TABLE 1 | Assessment tools for evaluating cognitive and global functioning in patients with MDD.

References	Acronym	Assessment tool	Characteristics	Target	Time need to be completed
Srisurapanont et al. (28)	MoCA	Montreal cognitive assessment	This scale can be divided into seven subtests, including visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation. The MoCA total score reflects the global cognitive performance.	Patients with MDD, patients with mild cognitive impairment	Unspecified, but it requires less time for completion than a complete set of neurocognitive tests
Harvey et al. (23)	UPSA	University of California San Diego performance-based skills assessment	It measures the everyday functioning skills in five function domains: comprehension/planning, finance, transportation, household, communication	Patients with MDD, patients with mild cognitive impairment	Unspecified
Ott et al. (29)	SCIP	Screen for cognitive impairment in psychiatry	SCIP consists of five subtests: verbal learning, working memory, verbal fluency, delayed memory, processing speed	Healthy controls, patients with bipolar disorder, MDD or schizophrenia	<20 min
Ott et al. (29)	COBRA	The cognitive complaints in bipolar disorder rating assessment	16-item self-reported instrument, which allows measure subjective cognitive dysfunctions including executive function, processing speed, working memory, verbal learning and memory, attention/concentration and mental tracking. The COBRA total score is obtained when the scores of each item are added up.	Patients with bipolar disorder, unipolar depression	Unspecified
McIntyre and Lee (24)	THINC-it Tool		It includes the 5-item Perceived Deficits Questionnaire (PDQ-5) and four traditional cognitive assessments.	Patients with MDD	10–15 min
IsHak et al. (30)	RI	Recovery index	It is based on a combination of the WSAS and Q-LES-Q scales, provides information on the level of social, personal, and work functioning. It can be calculated through accessing a web platform	Non-specific	Unspecified

of cognitive functioning on the global level of functioning of patients with MDD.

Some conventional antidepressants mitigate cognitive symptoms in people with depression, but a significant proportion of antidepressants inhibit cognitive functioning (40, 41). Recently, the CANMAT guidelines (2016) (42) suggested to tailor the pharmacological treatment on the basis of clinical specifiers. In particular, for patients with cognitive dysfunctions, the following pharmacological compounds should be preferred: Vortioxetine (Level 1), Bupropion (Level 2), Duloxetine (Level 2), SSRIs (Level 2). According to the CANMAT, only vortioxetine, an antidepressant agent (43, 44) with a multimodal action mediated by the combination of a direct effect on serotonin receptor activity and reuptake inhibition of SERT (45, 46), has level 1 of evidence compared to other antidepressants for managing cognitive dysfunction (47, 48). Compared to other antidepressant agents, patients treated with vortioxetine report better cognitive functioning (49), and this improvement is independent from the improvement of affective symptoms (13).

Drugs targeting multiple neurochemical systems simultaneously (e.g., serotonin–noradrenaline reuptake inhibitors) might be more likely to improve cognitive performance than treatments targeting a single system only (e.g., selective serotonin reuptake inhibitors) (50, 51). In particular, bupropion has been tested in improving memory and mental processing speed performance (52). Duloxetine has been proven to be effective in improving cognitive score as compared to placebo, and this change was found to be independent from the ameloriation of affective symptoms (53).

On the other hand, the antagonism on M1, H1, and α1 receptors (as observed in the case of TCAs) have been hypothesized as impacting negatively on cognitive functioning (54–56).

Although the pharmacological treatment is essential for the succesfull management of patients with MDD, the complete recovery is not guaranteed, as shown by the occurrence of relapses and recurrences (57). For this reason, psychosocial interventions, such as psychoeducation, cognitive remediation,

and cognitive-behavioral therapies, have been increasingly recognized as an essential component in the treatment of MDD, in association with pharmacological strategies (where needed), to achieve full recovery. In particular, it is necessary to integrate psychosocial treatment with pharmacological therapy, since these interventions are effective in improving the clinical course, treatment adherence, and psychosocial functioning of patients with MDD.

First-line psychological treatment recommendations for acute MDD include cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation (BA) (58). Whenever feasible, the combination of psychological interventions (CBT or IPT) with antidepressant treatment is recommended because combined treatment is superior to either treatment alone (58). First-line psychological treatments for maintenance phase include CBT and mindfulness-based cognitive therapy (MBCT). In order to select the type of psychosocial interventions, patient's preference for developing a personalized treatment plan shall be considered. A recent meta-analysis found that CBT is effective in patients with MDD, regardless of the baseline severity of the depressive episode, and can contribute to the achievement of full functional recovery (59). Several international guidelines suggest providing psychoeducational interventions to patients with MDD (60, 61). Different types of psychoeducational interventions are currently available, with the single-family approach, in which sessions are conducted with one family only, showing the most promising results (62). In particular, a systematic review has indicated that providing information about depression and its treatment is associated with a better prognosis and a reduction of family burden (63). Another psychosocial approach useful for achieving full functional recovery in patients with MDD is cognitive remediation (64–67). In particular, cognitive remediation—through the repeated activation of brain regions—can promote neuroplasticity, restoration of compromised neural processes, and improvement in neural function (68). Cognitive remediation programs include the repeated completion of cognitive tasks during several weeks. A recent meta-analysis (69) has confirmed that patients receiving this therapy report an improvement in attention, working memory and in the overall level of personal functioning. Furthermore, cognitive remediation seems to be the most promising intervention not only in improving cognitive functions, but also in improving depressive symptoms, contributing to the global recovery of the patients and to the full functional recovery (67). It is still debated the role of exercise interventions in improving cognitive functioning in patients with MDD (70). A recent meta-analysis (71) emphasized a lack of positive effect of physical exercise on cognition in patients with MDD. However, authors underlined that several limitations can have influenced their results, such as the small sample sizes of the included studies, the low dosage of physical exercises or the lack of cognitive assessment at baseline. Further studies are still needed in order to investigate the efficacy of psychosocial interventions, including physical activity component on cognitive functioning and full functional recovery of patients with MDD.

Other non-pharmacological strategies for improving cognitive symptoms in patients with MDD are repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) (72, 73). However, further studies are needed for evaluating the long-term efficacy of these treatments.

The present clinical review has some limitations which should be acknowledged. Given the nature of the included studies, we could not perform a meta-analysis, which would be however out of the scope of this paper. Moreover, this is not a systematic review, but it is rather a clinical review on recently developed assessment tools for evaluating psychosocial and cognitive functioning in patients with MDD. Another limitation is the short time frame for the inclusion of assessment tools. However, this methodological choice was made given the recent social and digital changes occurred in modern society. Finally, we did not search for gray literature, but we have focused on validated assessment tools only.

CONCLUSIONS

Several assessment tools are available for evaluating the cognitive functioning in patients with MDD. Nevertheless, there is the need to promote further studies adopting homogenous assessment instruments, in order to explore the objective and subjective cognitive functioning.

Longitudinal studies with representative sample and control groups are needed for assessing the effects of antidepressant therapy and compare groups of different ages and evaluating the impact of gender differences on cognitive function. Regarding the cognitive remediation approach, more longitudinal studies on a wider variety of treatments are needed. Since psychotherapeuthic approaches have been found to be effective in improving cognition, when associated with antidepressant drugs, it should be useful to clarify the specific role of each treatment in obtaining this improvement.

Another relevant aspect is that the same treatment will not work for all patients with MDD (74) and when defining the treatment programme of MDD depression, clinicians should consider to tailor it to patients' needs and preference and to adopt a shared-decision making style, which has been proven to be effective in improving long-term outcomes (75–81). Moreover, as recently pointed out in a survey involving all the categories of stakeholders of mental health, there is the need to include users' perspective in research studies (82–87), and people with MDD have their preferences on treatment choice and want to be actively involved in discussion about their care.

Finally, the most relevant clinical implication of assessing social and cognitive functioning in routine care may be the real shift in the management of patients with MDD from symptom remission to full functioning recovery.

AUTHOR CONTRIBUTIONS

The idea of the manuscript was conceived during a Lundbeck Advisory Board in 2017, attended by AF, BC, SDG, SLP, GM, ES,

AF and AV; with the exception of GS. AF wrote the first version of the manuscript; GS, BC, SDG, SLP, GM, ES, AT, AV and AF revised all manuscript drafts having full control over content.

FUNDING

The independent medical writing assistance was funded by Lundbeck Italy.

ACKNOWLEDGMENTS

Sheridan Henness, Ph.D. of Springer Healthcare Communications, prepared the second draft of this article under the direction of the authors, performed an English language edit, and prepared the manuscript for submission. Unconditional funding support for this editorial assistance was provided by Lundbeck Italy.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association (2013).
2. *Depression and Other Common Mental Disorders: Global Health Estimates*. Availble online at: http://apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2-eng.pdf
3. Bartoli F, Pompili M, Lillia N, Crocamo C, Salemi G, Clerici M, et al. Rates and correlates of suicidal ideation among stroke survivors: a meta-analysis. *J Neurol Neurosurg Psychiatry* (2017) 88:498–504. doi: 10.1136/jnnp-2017-315660
4. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health* (2013) 34:119–38. doi: 10.1146/annurev-publhealth-031912-114409
5. Friedrich MJ. Depression is the leading cause of disability around the world. *JAMA* (2017) 317:1517. doi: 10.1001/jama.2017.3826
6. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, Murray CJ, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. *PLoS Med*. (2013) 10:e1001547. doi: 10.1371/journal.pmed.1001547
7. Rush AJ. Distinguishing functional from syndromal recovery: implications for clinical care and research. *J Clin Psychiatry* (2015) 76:e832–4. doi: 10.4088/JCP.15com09859
8. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety* (2013) 30:515–27. doi: 10.1002/da.22063
9. Loos S, Clarke E, Jordan H, Puschner B, Fiorillo A, Luciano M, et al. Recovery and decision-making involvement in people with severe mental illness from six countries: a prospective observational study. *BMC Psychiatry* (2017) 17:38. doi: 10.1186/s12888-017-1207-4
10. Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Boerescu D, Attiullah N. Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. *Psychiatry Res*. (2006) 141:185–91. doi: 10.1016/j.psychres.2005.05.016
11. Trivedi MH. Evaluating and monitoring treatment response in depression using measurement-based assessment and rating scales. *J Clin Psychiatry* (2013) 74:e14. doi: 10.4088/JCP.12075tx2c
12. Habert J, Katzman MA, Oluboka OJ, McIntyre RS, McIntosh D, MacQueen GM, et al. Functional recovery in major depressive disorder: focus on early optimized treatment. *Prim Care Companion CNS Disord*. (2016) 18:5. doi: 10.4088/PCC.15r01926
13. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. (2014) 17:1557–67. doi: 10.1017/S1461145714000546
14. Lam RW, Filteau MJ, Milev R. Clinical effectiveness: the importance of psychosocial functioning outcomes. *J Affect Disord*. (2011) 132(Suppl. 1):S9–13. doi: 10.1016/j.jad.2011.03.046
15. Nil R, Lutolf S, Seifritz E. Residual symptoms and functionality in depressed outpatients: a one-year observational study in Switzerland with escitalopram. *J Affect Disord*. (2016) 197:245–50. doi: 10.1016/j.jad.2016.02.062
16. Papakostas GI. Major depressive disorder: psychosocial impairment and key considerations in functional improvement. *Am J Manag Care* (2009) 15(11 Suppl.):S316–21.
17. Kruijshaar ME, Hoeymans N, Bijl RV, Spijker J, Essink-Bot ML. Levels of disability in major depression: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord*. (2003) 77:53–64. doi: 10.1016/S0165-0327(02)00099-X
18. Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. (2012) 11:141–68. doi: 10.1038/nrd3628
19. McIntyre RS, Lee Y, Mansur RB. Treating to target in major depressive disorder: response to remission to functional recovery. *CNS Spectr*. (2015) 20(Suppl. 1):20–30; quiz 31. doi: 10.1017/S1092852915000826
20. Frampton JE. Vortioxetine: a review in cognitive dysfunction in depression. *Drugs* (2016) 76:1675–82. doi: 10.1007/s40265-016-0655-3
21. DeVane CL. Pharmacologic characteristics of ideal antidepressants in the 21st century. *J Clin Psychiatry* (2000) 61(Suppl. 11):4–8.
22. Bortolato B, Miskowiak KW, Kohler CA, Maes M, Fernandes BS, Berk M, et al. Cognitive remission: a novel objective for the treatment of major depression? *BMC Med*. (2016) 14:9. doi: 10.1186/s12916-016-0560-3
23. Harvey PD, Jacobson W, Zhong W, Nomikos GG, Cronquist Christensen M, Kurre Olsen C, et al. Determination of a clinically important difference and definition of a responder threshold for the UCSD performance-based skills assessment (UPSA) in patients with major depressive disorder. *J Affect Disord*. (2017) 213:105–11. doi: 10.1016/j.jad.2017.02.014
24. McIntyre RS, Lee Y. Cognition in major depressive disorder: a 'Systemically Important Functional Index' (SIFI). *Curr Opin Psychiatry* (2016) 29:48–55. doi: 10.1097/YCO.0000000000000221
25. Clausen M, Leppa S, Brown P, Sonderskov J, Panny M, Willenbacher W, et al. The combination of pixantrone, etoposide, bendamustine and, in CD20+ tumors, rituximab (PREBEN) shows promising feasibility/efficacy in heavily pre-treated aggressive lymphomas of B- and T-cell phenotype–results of the pre-trial experience leading to a Nordic Phase 1/2 study (the PREBEN trial). *Blood* (2016) 128:1782.
26. McIntyre RS, Best MW, Bowie CR, Carmona NE, Cha DS, Lee Y, et al. The THINC-Integrated Tool (THINC-it) screening assessment for cognitive dysfunction: validation in patients with major depressive disorder. *J Clin Psychiatry* (2017) 78:873–81. doi: 10.4088/JCP.16m11329
27. Cha DS, Carmona NE, Subramaniapillai M, Mansur RB, Lee Y, Hon Lee J, et al. Cognitive impairment as measured by the THINC-integrated tool (THINC-it): association with psychosocial function in major depressive disorder. *J Affect Disord*. (2017) 222:14–20. doi: 10.1016/j.jad.2017.06.036
28. Srisurapanont M, Eurviriyanukul K, Suttajit S, Varnado P. Internal consistency and concurrent validity of the Montreal Cognitive Assessment in individuals with major depressive disorder. *Psychiatry Res*. (2017) 253:333–7. doi: 10.1016/j.psychres.2017.04.014
29. Ott CV, Bjertrup AJ, Jensen JH, Ullum H, Sjælland R, Purdon SE, et al. Screening for cognitive dysfunction in unipolar depression: validation and evaluation of objective and subjective tools. *J Affect Disord*. (2016) 190:607–15. doi: 10.1016/j.jad.2015.10.059
30. IsHak WW, Bonifay W, Collison K, Reid M, Youssef H, Parisi T, et al. The recovery index: A novel approach to measuring recovery and predicting remission in major depressive disorder. *J Affect Disord*. (2017) 208:369–74. doi: 10.1016/j.jad.2016.08.081
31. Hammar A, Ardal G. Cognitive functioning in major depression–a summary. *Front Hum Neurosci*. (2009) 3:26. doi: 10.3389/neuro.09.026.2009

32. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med*. (2011) 41:1165–74. doi: 10.1017/S0033291710001911
33. Buist-Bouwman MA, Ormel J, de Graaf R, de Jonge P, van Sonderen E, Alonso J, et al. Mediators of the association between depression and role functioning. *Acta Psychiatr Scand*. (2008) 118:451–8. doi: 10.1111/j.1600-0447.2008.01285.x
34. Clark M, DiBenedetti D, Perez V. Cognitive dysfunction and work productivity in major depressive disorder. *Expert Rev Pharmacoecon Outcomes Res*. (2016) 16:455–63. doi: 10.1080/14737167.2016.1195688
35. Stewart WF, Ricci JA, Chee E, Hahn SR, Morganstein D. Cost of lost productive work time among US workers with depression. *JAMA* (2003) 289:3135–44. doi: 10.1001/jama.289.23.3135
36. Woo YS, Rosenblat JD, Kakar R, Bahk WM, McIntyre RS. Cognitive deficits as a mediator of poor occupational function in remitted major depressive disorder patients. *Clin Psychopharmacol Neurosci*. (2016) 14:1–16. doi: 10.9758/cpn.2016.14.1.1
37. Saragoussi D, Touya M, Haro JM, Jonsson B, Knapp M, Botrel B, et al. Factors associated with failure to achieve remission and with relapse after remission in patients with major depressive disorder in the PERFORM study. *Neuropsychiatr Dis Treat*. (2017) 13:2151–65. doi: 10.2147/NDT.S136343
38. Baune BT, Renger L. Pharmacological and non-pharmacological interventions to improve cognitive dysfunction and functional ability in clinical depression–a systematic review. *Psychiatry Res*. (2014) 219:25–50. doi: 10.1016/j.psychres.2014.05.013
39. Van RheenenTE, Rossel EL. An empirical evaluation of the MATRICS consensus cognitive battery in bipolar disorder. *Bipolar Disord*. (2014) 16:318–25. doi: 10.1111/bdi.12134
40. Biringer E, Rongve A, Lund A. A review of modern antidepressants effects on neurocognitive function. *Curr Psychiatr Rev*. (2009) 5:164–74. doi: 10.2174/157340009788971137
41. Sayyah M, Eslami K, AlaiShehni S, Kouti L. Cognitive function before and during treatment with selective serotonin reuptake inhibitors in patients with depression or obsessive-compulsive disorder. *Psychiatry J*. (2016) 2016:5480391. doi: 10.1155/2016/5480391
42. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, et al. CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 3. pharmacological treatments. *Can J Psychiatry* (2016) 61:540–60. doi: 10.1177/0706743716659417
43. Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol*. (2014) 29:138–49. doi: 10.1097/YIC.0000000000000018
44. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry* (2012) 73:953–9. doi: 10.4088/JCP.11m07470
45. Bang-Andersen B, Ruhland T, Jorgensen M, Smith G, Frederiksen K, Jensen KG, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. *J Med Chem*. (2011) 54:3206–21. doi: 10.1021/jm101459g
46. Westrich L, Sprouse J, Sanchez C. The effects of combining serotonin reuptake inhibition and 5-HT7 receptor blockade on circadian rhythm regulation in rodents. *Physiol Behav*. (2013) 110–11:42–50. doi: 10.1016/j.physbeh.2012.12.009
47. Bortolato B, Carvalho AF, McIntyre RS. Cognitive dysfunction in major depressive disorder: a state-of-the-art clinical review. *CNS Neurol Disord Drug Targets* (2014) 13:1804–18. doi: 10.2174/1871527313666141130203823
48. Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): actions at serotonin receptors may enhance downstream release of four pro-cognitive neurotransmitters. *CNS Spectr*. (2015) 20:515–9. doi: 10.1017/S1092852915000358
49. Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology* (2015) 40:2025–37. doi: 10.1038/npp.2015.52
50. Stahl SM. Enhancing outcomes from major depression: using antidepressant combination therapies with multifunctional pharmacologic mechanisms from the initiation of treatment. *CNS Spectr*. (2010) 15: 79–94. doi: 10.1017/S1092852900027334
51. McLennan SN, Mathias JL. The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry* (2010) 25:933–44. doi: 10.1002/gps.2431
52. Herrera-Guzmán I, Herrera-Abarca JE, Gudayol-Ferré E, Herrera-Guzmán D, Gómez-Carbajal L, Peña-Olvira M, et al. Effects of selective serotonin reuptake and dual serotonergic-noradrenergic reuptake treatments on attention and executive functions in patients with major depressive disorder. *Psychiatry Res*. (2010) 177:323–9. doi: 10.1016/j.psychres.2010.03.006
53. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry* (2007) 164:900–9. doi: 10.1176/ajp.2007.164.6.900
54. Doraiswamy PM, Krishnan KR, Oxman T, Jenkyn LR, Coffey DJ, Burt T, et al. Does antidepressant therapy improve cognition in elderly depressed patients? *J Gerontol A Biol Sci Med Sci*. (2003) 58:M1137–44.
55. Culang-Reinlieb ME, Sneed JR, Keilp JG, Roose SP. Change in cognitive functioning in depressed older adults following treatment with sertraline or nortriptyline. *Int J Geriatr Psychiatry* (2012) 27:777–84. doi: 10.1002/gps.2783
56. Huang YJ, Lane HY, Lin CH. New treatment strategies of depression: based on mechanisms related to neuroplasticity. *Neural Plast*. (2017) 2017:4605971. doi: 10.1155/2017/4605971
57. Cuijpers P, Cristea IA, Karyotaki E, Reijnders M, Huibers MJ. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry* (2016) 15:245–58. doi: 10.1002/wps.20346
58. Parikh SV, Quilty LC, Ravitz P, Rosenbluth M, Pavlova B, Grigoriadis S, et al. CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 2. Psychological treatments. *Can J Psychiatry* (2016) 61:524–39. doi: 10.1177/0706743716659418
59. Furukawa TA, Weitz ES, Tanaka S, Hollon SD, Hofmann SG, Andersson G, et al. Initial severity of depression and efficacy of cognitive-behavioural therapy: individual-participant data meta-analysis of pill-placebo-controlled trials. *Br J Psychiatry* (2017) 210:190–6. doi: 10.1192/bjp.bp.116.187773
60. Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry* (2015) 49:1–85. doi: 10.1177/0004867415617657
61. *Depression In Adults: Recognition And Management*. Available online at: https://www.nice.org.uk/guidance/cg90
62. Luciano M, Del Vecchio V, Giacco D, De Rosa C, Malangone C, Fiorillo A. A 'family affair'? The impact of family psychoeducational interventions on depression. *Expert Rev Neurother*. (2012) 12:83–91; quiz 92. doi: 10.1586/ern.11.131
63. Tursi MF, Baes C, Camacho FR, Tofoli SM, Juruena MF. Effectiveness of psychoeducation for depression: a systematic review. *Aust N Z J Psychiatry* (2013) 47:1019–31. doi: 10.1177/0004867413491154
64. Bowie CR, Gupta M, Holshausen K, Jokic R, Best M, Milev R. Cognitive remediation for treatment-resistant depression: effects on cognition and functioning and the role of online homework. *J Nerv Ment Dis*. (2013) 201:680–5. doi: 10.1097/NMD.0b013e31829c5030
65. Miskowiak KW, Ott CV, Petersen JZ, Kessing LV. Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. *Eur Neuropsychopharmacol*. (2016) 26:1845–67. doi: 10.1016/j.euroneuro.2016.09.641
66. Pybis J, Saxon D, Hill A, Barkham M. The comparative effectiveness and efficiency of cognitive behaviour therapy and generic counselling in the treatment of depression: evidence from the 2nd UK National Audit of psychological therapies. *BMC Psychiatry* (2017) 17:215. doi: 10.1186/s12888-017-1370-7

67. Trapp W, Engel S, Hajak G, Lautenbacher S, Gallhofer B. Cognitive remediation for depressed inpatients: results of a pilot randomized controlled trial. *Aust N Z J Psychiatry* (2016) 50:46–55. doi: 10.1177/0004867415622271
68. Maples NJ, Velligan DI. Cognitive adaptation training: establishing environmental supports to bypass cognitive deficits and improve functional outcomes. *Am J Psychiatr Rehabil.* (2008) 11:164–80. doi: 10.1080/15487760801963686
69. Motter JN, Pimontel MA, Rindskopf D, Devanand DP, Doraiswamy PM, Sneed JR. Computerized cognitive training and functional recovery in major depressive disorder: a meta-analysis. *J Affect Disord.* (2016) 189:184–91. doi: 10.1016/j.jad.2015.09.022
70. Sun M, Lanctot K, Herrmann N, Gallagher D. Exercise for cognitive symptoms in depression: a systematic review of interventional studies. *Can J Psychiatry* (2017) 1:706743717738493. doi: 10.1177/0706743717738493
71. De Rosa C, Sampogna G, Luciano M, Del Vecchio V, Pocai B, Borriello G, et al. Improving physical health of patients with severe mental disorders: a critical review of lifestyle psychosocial interventions. *Expert Rev Neurother.* (2017) 17:667–81. doi: 10.1080/14737175.2017.1325321
72. Tortella G, Selingardi PM, Moreno ML, Veronezi BP, Brunoni AR. Does non-invasive brain stimulation improve cognition in major depressive disorder? A systematic review. *CNS Neurol Disord Drug Targets* (2014) 13:1759–69.
73. Serafini G, Pompili M, Belvederi Murri M, Respino M, Ghio L, Girardi P, et al. The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. A systematic review. *Neuropsychobiology* (2015) 71:125–39. doi: 10.1159/000381351
74. MacQueen GM, Memedovich KA. Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. *Psychiatry Clin Neurosci.* (2017) 71:18–27. doi: 10.1111/pcn.12463
75. Coulter A. Shared decision making: everyone wants it, so why isn't it happening? *World Psychiatry* (2017) 16:117–8. doi: 10.1002/wps.20407
76. Slade M. Implementing shared decision making in routine mental health care. *World Psychiatry* (2017) 16:146–153. doi: 10.1002/wps.20412
77. Tse S. Shared decision making in mental health care settings: perspective, purpose and practice. *World Psychiatry* (2017) 16:158–160. doi: 10.1002/wps.20417
78. McCabe R. Involvement in decision making: the devil is in the detail. *World Psychiatry* (2017) 16:155–6. doi: 10.1002/wps.20414
79. Scholl I, Barr PJ. Incorporating shared decision making in mental health care requires translating knowledge from implementation science. *World Psychiatry* (2017) 16:160–1. doi: 10.1002/wps.20418
80. Freidl M, Pesola F, Konrad J, Puschner B, Kovacs AI, De Rosa C, et al. Effects of clinical decision topic on patients' involvement in and satisfaction with decisions and their subsequent implementation. *Psychiatr Serv.* (2016) 67:658–63. doi: 10.1176/appi.ps.201500083
81. Puschner B, Becker T, Mayer B, Jordan H, Maj M, Fiorillo A, et al. Clinical decision making and outcome in the routine care of people with severe mental illness across Europe (CEDAR). *Epidemiol Psychiatr Sci.* (2016) 25:69–79. doi: 10.1017/S204579601400078X
82. Fiorillo A, Luciano M, Del Vecchio V, Sampogna G, Obradors-Tarragó C, Maj M, et al. Priorities for mental health research in Europe: a survey among national stakeholders' associations within the ROAMER project. *World Psychiatry* (2013) 12:165–70. doi: 10.1002/wps.20052
83. Forsman AK, Wahlbeck K, Aarø LE, Alonso J, Barry MM, Brunn M, et al. Research priorities for public mental health in Europe: recommendations of the ROAMER project. *Eur J Public Health* (2015) 25:249–54. doi: 10.1093/eurpub/cku232
84. Wykes T, Haro JM, Belli SR, Obradors-Tarragó C, Arango C, Ayuso-Mateos JL, et al. Mental health research priorities for Europe. *Lancet Psychiatry* (2015) 2:1036–42. doi: 10.1016/S2215-0366(15)00332-6
85. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. *CNS Drugs* (2010) 24:267–84. doi: 10.2165/11530230-000000000-00000
86. Demyttenaere K. Taking the depressed "person" into account before moving into personalized or precision medicine. *World Psychiatry* (2016) 15:236–7. doi: 10.1002/wps.20362
87. Uher R. Person-centered measurement-based care for depression. *World Psychiatry* (2016) 15:238–9. doi: 10.1002/wps.20363

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer NY and handling Editor declared their shared affiliation.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 16 October 2018
doi: 10.3389/fpsyt.2018.00482

A Dissociation of the Acute Effects of Bupropion on Positive Emotional Processing and Reward Processing in Healthy Volunteers

Annabel E. L. Walsh[1,2], *Nathan T. M. Huneke*[2,3], *Randi Brown*[2], *Michael Browning*[2,4], *Phil Cowen*[2] *and Catherine J. Harmer*[1,2]*

[1] NIHR Oxford Health Biomedical Research Centre, Warneford Hospital, Oxford, United Kingdom, [2] Psychopharmacology and Emotion Research Laboratory, Department of Psychiatry, University of Oxford, Oxford, United Kingdom, [3] University Department of Psychiatry, University of Southampton, Southampton, United Kingdom, [4] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom

OPEN ACCESS

Edited by:
Gianluca Serafini,
Ospedale San Martino (IRCCS), Italy

Reviewed by:
Célia Fourrier,
University of Adelaide, Australia
Matthew James Knight,
University of Adelaide, Australia

***Correspondence:**
Catherine J. Harmer
catherine.harmer@psych.ox.ac.uk

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: 19 July 2018
Accepted: 13 September 2018
Published: 16 October 2018

Citation:
Walsh AEL, Huneke NTM, Brown R, Browning M, Cowen P and Harmer CJ (2018) A Dissociation of the Acute Effects of Bupropion on Positive Emotional Processing and Reward Processing in Healthy Volunteers. Front. Psychiatry 9:482. doi: 10.3389/fpsyt.2018.00482

Background: Previous research indicates that antidepressants can restore the balance between negative and positive emotional processing early in treatment, indicating a role of this effect in later mood improvement. However, less is known about the effect of antidepressants on reward processing despite the potential relevance to the treatment of anhedonia. In this study, we investigated the effects of an acute dose of the atypical antidepressant (dual dopamine and noradrenaline reuptake inhibitor) bupropion on behavioral measures of emotional and reward processing in healthy volunteers.

Methods: Forty healthy participants were randomly allocated to double-blind intervention with either an acute dose of bupropion or placebo prior to performing the Emotional Test Battery (ETB) and a probabilistic instrumental learning task.

Results: Acute bupropion significantly increased the recognition of ambiguous faces as happy, decreased response bias toward sad faces and reduced attentional vigilance for fearful faces compared to placebo. Bupropion also reduced negative bias compared to placebo in the emotional recognition memory task (EMEM). There was no evidence that bupropion enhanced reward processing or learning. Instead, bupropion was associated with reduced likelihood to choose high-probability wins and increased score on a subjective measure of anhedonia.

Conclusions: Whilst acute bupropion decreases negative and increases positive emotional processing, it has an adverse effect on reward processing. There seems to be a dissociation of the acute effects of bupropion on positive emotional processing and reward processing, which may have clinical implications for anhedonia early in treatment.

Keywords: emotion, antidepressants, dopamine, reward, depression, anhedonia

INTRODUCTION

Patients suffering from major depressive disorder (MDD) display negative biases in emotional processing across a range of cognitive domains, including perception, attention, and memory (1–4). The neuropsychological theory of antidepressant action hypothesizes that the direct action of antidepressants is to decrease negative emotional processing and increase positive emotional processing early in treatment, prior to any mood improvement, indicating a role of this change in the therapeutic effect of the antidepressant (4–7). Indeed, acute or 7 day administration of the selective serotonin reuptake inhibitor citalopram or the noradrenaline reuptake inhibitor reboxetine was found to increase the recall of positive self-referent words and the perception of ambiguous faces as happy in both healthy volunteers (8–10) and MDD patients (11) in the absence of any changes in mood.

The majority of research on the effects of antidepressants has been conducted using selective serotonin and/or noradrenaline reuptake inhibitors (SSRIs/SNRIs) and several questions remain. Firstly, MDD is not only characterized by low mood but also a loss of interest or pleasure in previously enjoyed activities, known as anhedonia. It is becoming clearer that whilst SSRIs or SNRIs reduce negative biases in emotional processing to improve low mood, they do not fully correct the experience of anhedonia (12) and may actually exacerbate reward deficits (13). Pre-clinical, physiological studies evidence a role of dopamine in reward (14, 15). Therefore, it has been hypothesized that anhedonia and abnormal reward-based decision making in probabilistic instrumental learning tasks observed in MDD (16–18) involve changes in the dopamine system. Indeed, an acute dose of a dopaminergic enhancing drug (L-DOPA) has previously been found to increase the likelihood of choosing high-probability wins during a probabilistic instrumental learning task compared to a dopamine antagonist (haloperidol) in healthy volunteers (19). It has therefore been suggested that atypical, dopaminergic antidepressants may act on such aberrant reward processing and be better suited to treat anhedonia (12).

It is unclear whether positive emotional processing and reward processing are different expressions of the same underlying system (20), or whether they are independent processes in the manifestation of the symptom clusters in MDD. As such, emotional and reward processing may be either similarly or differentially affected by antidepressants with an effect on dopamine function such as bupropion, a dual dopamine and noradrenaline reuptake inhibitor.

Therefore, here we investigated the acute effects of bupropion compared to placebo on commonly used behavioral measures of emotional and reward processing in healthy volunteers. Specifically, we aimed to investigate whether bupropion has similar effects to SSRIs and/or SNRIs acting to reduce negative biases in emotional processing, or has more specific effects on positive emotional or reward processing. Since bupropion increases dopamine function, we hypothesized that it would specifically increase positive emotional processing and reward sensitivity in a probabilistic instrumental learning task.

MATERIALS AND METHODS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent.

Participant Recruitment, Screening, and Randomization

A reverse power calculation using the effect sizes observed in preceding studies of other antidepressants [e.g., (8, 9)] indicated a sample size of 20 participants per treatment group would be sufficient to detect a significant difference between the two treatment groups with a power of 0.95. Therefore, a total of 40 healthy participants were recruited and deemed to be free from either current or past history of any Axis 1 DSM-IV psychiatric illness via assessment with the Structured Clinical Interview (SCID) for DSM-IV (21). They also had no physical medical conditions, were free of any medications or drugs that could impact upon the safety or effect of bupropion for at least 3 weeks and naive to the behavioral tasks.

Participants were randomly allocated to double-blind intervention with either an acute dose (150 mg) of sustained release bupropion or placebo. Administration of the treatment in identical capsules by an independent member of staff ensured that both the participant and investigator remained blind to the treatment received. Participants were stratified for gender and matched for age and National Adult Reading Test (NART)-derived verbal IQ (22). Note that an additional group of 20 participants were also recruited and randomized to a no treatment group to assess the influence of the placebo effect, the results of which are reported in Huneke et al. (23); however, all hypotheses for both studies were made a priori.

A 3 h wait period followed treatment administration since this is the t_{max} of the sustained release formulation of bupropion and allowed for testing at maximum plasma concentration (24). Participants then completed the Emotional Test Battery (ETB) and a probabilistic instrumental learning task to assess emotional and reward processing. Subjective mood was also assessed via completion of a variety of questionnaires before and after treatment administration and behavioral assessment. Firstly, the Hamilton Rating Scale for Depression (HAM-D) (25) was administered via a semi-structured interview with a trained experimenter. The rest of the questionnaires were self-report questionnaires completed on a computer and included the Adult Eysenck Personality Questionnaire (EPQ) (26), the Full Mood and Anxiety Symptom Questionnaire (MASQ), the Positive and Negative Affect Schedule (PANAS) (27), the Befindlichkeits Scale (BFS) (28), the Snaith-Hamilton Pleasure Scale (SHAPS) (29), and a side-effects questionnaire listing the side-effects most common for bupropion. The SHAPS comprises 14 items with each item describing a pleasurable situation covering one of four domains of pleasure: interests / pastimes, social interaction, sensory experience and food/drink, with a higher score indicating higher anhedonia. After treatment administration and behavioral

assessment, participants repeated the PANAS, BFS, SHAPS, and side-effects questionnaires.

Emotional Test Battery

The ETB (P1vital, Oxford, UK) is designed to assess the processing of a variety of affectively valenced stimuli and comprises five validated, computerized cognitive tasks named as follows: Facial Expression Recognition Task (FERT), Emotional Categorization Task (ECAT), Facial Dot-Probe Task (FDOT), Emotional Recall Task (EREC), and Emotional Recognition Memory Task (EMEM). These tasks have previously been described in full (11, 30). "In brief, the FERT comprises a series of facial expressions associated with six basic emotions: anger, disgust, fear, happy, sad and surprise at a range of different intensity levels and participants are required to identify the emotion of the face. Signal detection theory is used to provide estimates of target sensitivity (d') and beta. The ECAT comprises a series of positively and negatively valenced self-referent words and participants are required to indicate whether they would like or dislike to be referred to as each word. In the FDOT, the attentional vigilance to happy or fearful faces can be determined from participants' response latency to indicate the alignment of a dot probe appearing in the place of one of the faces. The EREC is a surprise free recall task during which participants are required to remember as many of the positively and negatively valenced self-referent words from the ECAT as they can in 2 min. Finally, the EMEM comprises self-referent words from the ECAT and previously unseen self-referent words that participants are required to classify as familiar or novel" (30). Further details for each task are provided in the **Supplementary Material**.

Probabilistic Instrumental Learning Task

The probabilistic instrumental learning task was a modified version of that described in Pessiglione et al. (19) and has previously been described in full (30). "Task stimuli consisted of two pairs of symbols with one pair associated with win outcomes (win £1 or no change) and the other associated with loss outcomes (lose £1 or no change). Each symbol in the pair corresponded to reciprocal probabilities (0.7 or 0.3) of the associated outcomes occurring.

Participants first performed a shortened, 10 trial familiarization version of the task. Participants then performed two 60 trial runs (30 win trials and 30 loss trials) with each run containing a different set of 4 symbols. Participants began the task with £5. On each trial, participants were randomly presented with a pair of symbols on a display screen for 4,000 ms, with each symbol randomly positioned either to the left or the right of a central fixation cross. Participants were required to choose between the two symbols in order to maximize their winnings. Once a choice was made, outcome feedback was provided. Participants should use the outcome feedback to gradually learn the symbol-outcome associations over time, such that they consistently choose the symbol with the high-probability win and avoid the symbol with the high-probability loss. Outcome measures were end total, amount won and amount lost, choice frequency and reaction time averaged across the two runs."

Statistics

Reaction times for all tasks (with the exception of the EREC where a 2 min time limit is imposed) were trimmed at the participant level: reaction times above 3 standard deviations from the mean or below 200 ms were excluded prior to calculating the mean. Data for all tasks was normally distributed allowing the use of parametric statistical tests.

Data from each task of the ETB was analyzed using a repeated measures analysis of variance (ANOVA) with treatment group (bupropion, placebo) as the between-subject factor and different within-subject factors depending on the task (FERT: face emotion; ECAT/EREC/EMEM: word valence; FDOT: face emotion, masking). Significant interactions were followed up with independent samples *t*-tests between the two treatment groups. Since previous studies have found both citalopram and reboxetine to increase the perception of ambiguous faces as happy in both healthy volunteers (8–10) and MDD patients (11), a planned comparison of the recognition of happy faces between groups was completed for the FERT.

For the probabilistic instrumental learning task, participants totaling less than the initial £5 were assumed to not have understood the task and were excluded (6 in total: 3 from the bupropion group and 3 from the placebo group). Data was then averaged across the two runs and analyzed using independent samples *t*-tests between the two treatment groups.

RESULTS

Participant Demographics and Characterization

There were no significant differences between treatment groups with regards to gender, age, NART-derived verbal IQ and baseline scores on the HAM-D and self-report questionnaires (**Table S1**).

Changes in Subjective Mood

There were no significant main effects of treatment group or time by treatment group interactions for any of the questionnaires measuring subjective mood, apart from the SHAPS. A time by treatment group interaction was observed for the SHAPS [$F_{(1\,38)} = 5.95$, $p < 0.05$] with a significant difference in the change in SHAPS score over time between the placebo and bupropion groups [$t_{(38)} = -2.44$, $p < 0.05$]. Paired *t*-tests found SHAPS score to decrease in the placebo group, although not significantly (-1.25 ± 3.77, $p = 0.15$), but increase in the bupropion group with a trend toward significance ($+1.40 \pm 3.17$, $p = 0.06$). Side-effect ratings were very low with the majority of participants rating that side-effects were absent (1.00) pre- and post-treatment (**Table S2**).

Acute Effects of Bupropion on Emotional Processing

Facial Expression Recognition Task

During the FERT, participants are required to recognize emotional facial expressions. Signal detection theory is used to provide estimates of target sensitivity (d') and beta. For % accuracy in recognizing emotional facial expressions, there was no significant main effect of treatment group [$F_{(1,\,38)} = 0.97$, $p =$

0.33] or face emotion by treatment group interaction [$F_{(5, 190)} = 0.89$, $p = 0.49$]. Correspondingly, there was also no significant main effect of treatment group [$F_{(1, 38)} = 1.00$, $p = 0.32$] or face emotion by treatment group interaction [$F_{(5, 190)} = 0.43$, $p = 0.83$] for d'. In a planned comparison of the recognition of happy faces between groups, the bupropion group were found to show significantly higher % accuracy [$t_{(38)} = -2.33$, $p < 0.05$] and d' [$t_{(38)} = -2.18$, $p < 0.05$] for happy faces than the placebo group (**Figure 1B**). Furthermore, a significant intensity of face emotion by treatment group interaction was found for the % accuracy for recognizing happy faces [$F_{(9, 342)} = 3.14$, $p < 0.01$], with the bupropion group displaying significantly higher % accuracy for recognizing happy faces at lower intensities than the placebo group [30% happiness intensity: $t_{(38)} = -2.45$, $p < 0.05$; 40% happiness intensity: $t_{(38)} = -2.73$, $p < 0.01$] (**Figure 1A**). There was a trend toward significance for a face emotion by treatment group interaction for beta [$F_{(5, 185)} = 2.17$, $p = 0.06$] with independent *t*-tests finding an effect of treatment group on the beta for sad faces only. The bupropion group displayed a significantly higher beta value for sad faces compared to the placebo group [$t_{(38)} = -2.32$, $p < 0.05$], indicating bupropion may induce a response bias away from sad faces (**Figure 1C**).

There was no significant main effect of treatment group [$F_{(1, 37)} = 0.01$, $p = 0.94$] or face emotion by treatment group interaction [$F_{(5, 185)} = 0.35$, $p = 0.88$] for reaction time.

Emotional Categorization Task

During the ECAT, participants are required indicate as quickly as they can whether they would like or dislike to be referred to as various positively and negatively valenced words. There was no significant main effect of treatment group [$F_{(1, 38)} = 3.11$, $p = 0.09$] or word valence by treatment group interaction [$F_{(1, 38)} = 0.01$, $p = 0.91$] for reaction time.

Facial Dot-Probe Task

In the FDOT, the attentional vigilance to happy or fearful faces can be determined from participants' response latency to indicate the alignment of a dot probe appearing in the place of one of the faces. There was a significant face emotion by masking by treatment group interaction for attentional vigilance [$F_{(1, 38)} = 5.45$, $p < 0.05$]. This was found to be driven by a significant face emotion by treatment group interaction for unmasked faces [$F_{(1, 38)} = 4.30$, $p < 0.05$], with the bupropion group displaying significantly reduced explicit attentional vigilance for unmasked fearful faces compared to the placebo group [$t_{(38)} = 2.00$, $p < 0.05$] (**Figure 2**).

Emotional Recall Task

The EREC is a surprise free recall task during which participants are required to remember as many of the positively and negatively valenced self-referent words from the ECAT as they can in 2 min. There was no significant main effect of treatment group or word valence by treatment group interaction for both number of words correctly [$F_{(1, 38)} = 1.22$, $p = 0.28$; $F_{(1, 38)} = 2.00$, $p = 0.17$] and falsely [$F_{(1, 38)} = 0.17$, $p = 0.68$; $F_{(1, 38)} = 0.38$, $p = 0.54$] recalled.

Emotional Recognition Memory Task

The EMEM comprises the words from the ECAT and previously unseen words that participants are required to classify as familiar or novel. A significant word valence by treatment group interaction was found for both novel words misclassified as familiar [$F_{(1, 38)} = 10.24$, $p < 0.01$] and familiar words misclassified as novel [$F_{(1, 38)} = 7.34$, $p < 0.01$]. **Figure 3A** suggests that bupropion increases the familiarity of positive words and decreases the familiarity of negative words. When considering just false alarms (novel words misclassified as familiar), there was no significant difference between groups for positive words [$t_{(38)} = 0.65$, $p = 0.52$] but the bupropion group displayed significantly increased beta for negative words compared to the placebo group [$t_{(38)} = -2.25$, $p < 0.05$] (**Figure 3B**).

Acute Effects of Bupropion on Reward Processing

Independent samples *t*-tests did not find a significant difference between treatment groups for the total monetary amount at the end of the task [$t_{(38)} = -0.51$, $p = 0.61$], the amount won [$t_{(38} = 0.20$, $p = 0.85$] or the amount lost [$t_{(38)} = -1.18$, $p = 0.24$] (**Figure 4A**). A repeated measures ANOVA did find a task condition by treatment group interaction for reaction time [$F_{(1, 38)} = 5.73$, $p < 0.05$], with the bupropion group displaying slower reaction times in the win vs. loss condition compared to the placebo group (**Figure 4B**).

In order to provide more temporal information about reward learning differences between treatment groups, learning curves were produced for each treatment group depicting trial-by-trial the proportion of participants that chose the correct symbol in the win condition, associated with high-probability win and the incorrect symbol in the loss condition, associated with high-probability loss (**Figure 5A**). Both treatment groups learnt to choose the high-probability win and avoid the high-probability loss by about trial 10. To assess reward sensitivity after learning, the proportion of participants choosing the correct symbol in the win and loss conditions was averaged over the remaining 20 trials of the task where learning had plateaued (31). The bupropion group was found to be significantly less likely to choose the correct symbol in the win condition compared to placebo [$t_{(38)} = 3.00$, $p < 0.01$] (**Figure 5B**).

DISCUSSION

The present study aimed to investigate whether bupropion has similar effects to SSRIs and/or SNRIs acting to reduce negative biases in emotional processing, or has more specific effects on positive emotional or reward processing. Since bupropion increased dopamine function, we hypothesized that it would specifically increase positive emotional processing and reward sensitivity on a probabilistic instrumental learning task similarly to other dopamine acting drugs (19). An acute dose of bupropion significantly increased the recognition of ambiguous faces as happy, decreased response bias toward sad faces and reduced attentional vigilance for fearful faces compared to placebo. Bupropion also reduced negative bias compared to placebo in the (EMEM). There was no evidence that bupropion enhanced

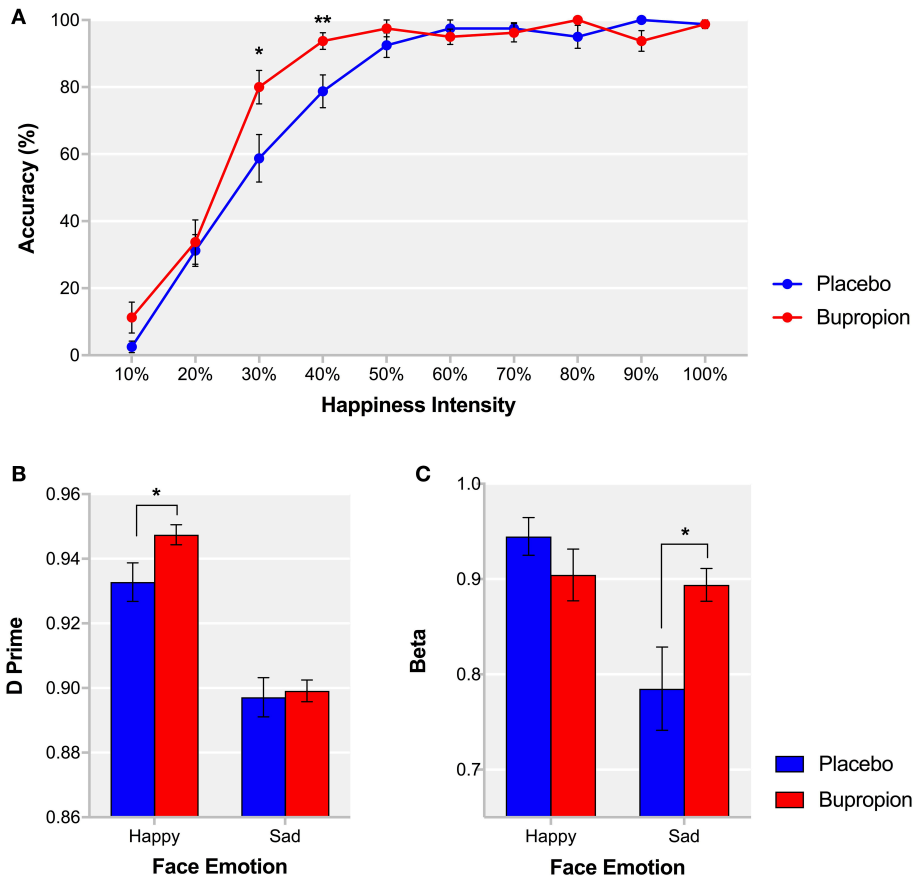

FIGURE 1 | FERT **(A)** % accuracy for each happiness intensity and signal detection derived **(B)** d' and **(C)** beta for happy and sad faces for each treatment group. Values are reported as means ± SEM. Asterisks denote the degree of significance obtained for planned comparisons (*$p < 0.05$, **$p < 0.01$).

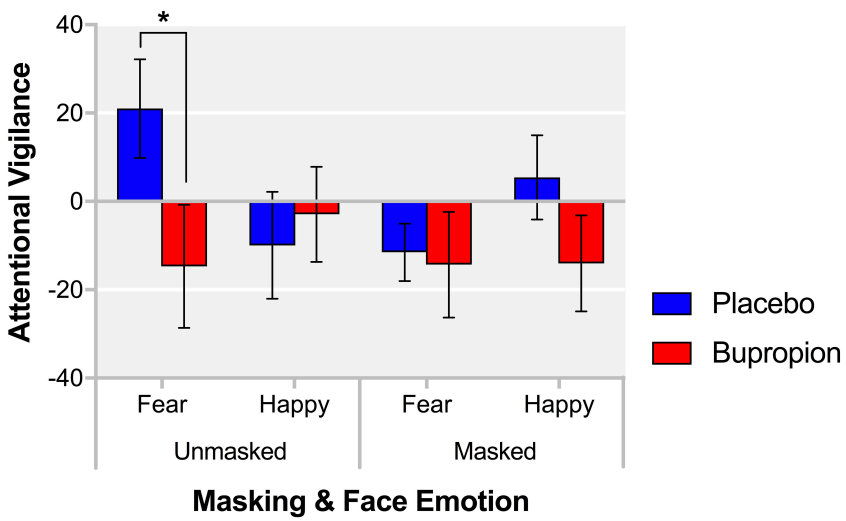

FIGURE 2 | FDOT attentional vigilance for each masking and face emotion condition for each treatment group. Values are reported as means ± SEM. Asterisks denote the degree of significance obtained for planned comparisons (*$p < 0.05$).

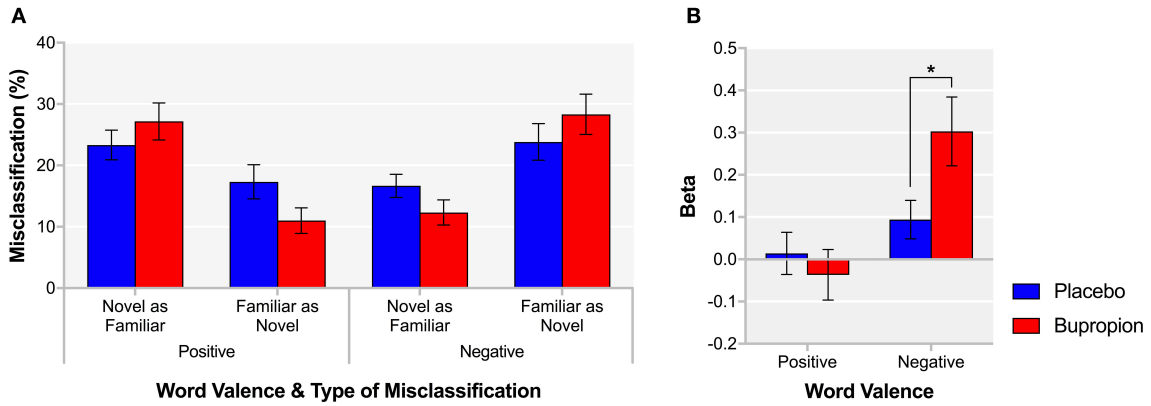

FIGURE 3 | EMEM **(A)** % misclassification and **(B)** beta for each word valence and treatment group. Values are reported as means ± SEM. Asterisks denote the degree of significance obtained for planned comparisons (*$p < 0.05$).

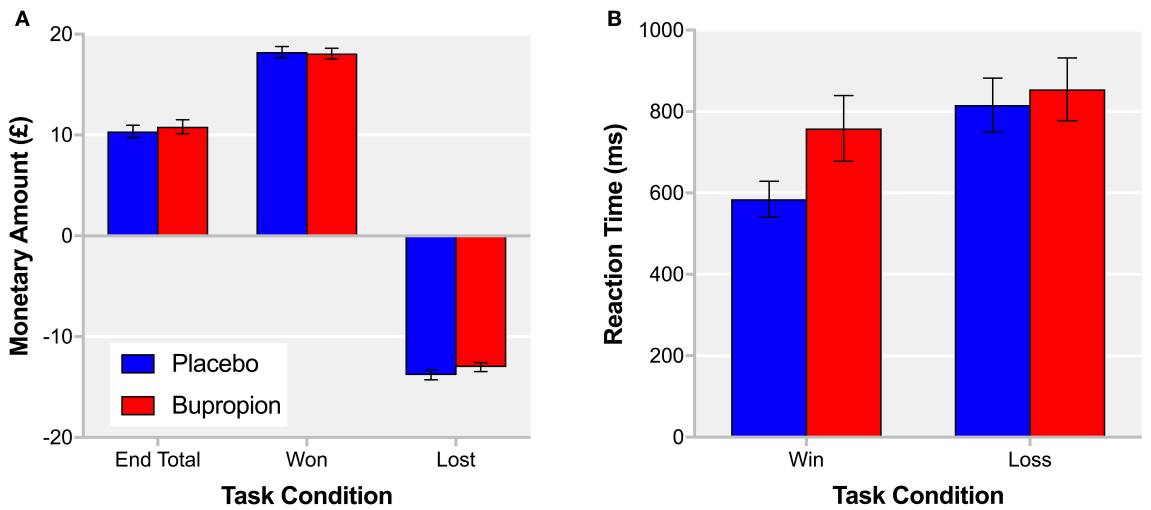

FIGURE 4 | (A) End total, amount won and amount lost and **(B)** reaction time for the win and loss conditions of the probabilistic instrumental learning task for each treatment group. Values are reported as means ± SEM.

reward processing or learning; rather the drug treatment was associated with reduced sensitivity to high-probability wins and increase in score on a subjective measure of anhedonia compared to placebo.

Emotional Processing

Whilst an acute dose of bupropion did produce a slight increase in positive emotional processing, with an increase in the recognition of ambiguous faces as happy, it was actually found to have stronger effects on decreasing negative emotional processing, with a decrease in the response bias for sad faces, attentional vigilance to fearful faces and negative bias in emotional recognition compared to placebo. These effects on emotional processing are similar to those seen with SSRIs and/or SNRIs (8–10) and have been hypothesized to be an early mechanism of antidepressant drug action; by reversing negative biases in depression and reducing the influence of this maintaining factor (4–7).

The profile of effects overlaps with the effects of SNRIs to a greater extent than SSRIs (6). Specifically, in addition to the positive biasing effect, SSRIs paradoxically increase fear processing early in treatment. For example, an acute dose of the SSRI citalopram was found to increase the startle response (32) and the recognition of fearful faces (33). However, an acute dose of the SNRI reboxetine was not found to have any effect on fear processing (9), similarly to bupropion in the present study. Reboxetine has also been found to increase the recognition of happy faces in the FERT and alter the balance of memory for self-referent words, causing an increase in recall of positive words or decrease in the recall of negative words (9–11). Whilst reboxetine acts primarily as an SNRI, some have reported that it also increases dopaminergic activity in the frontal cortex (34, 35). Likewise, although dopamine reuptake inhibition is the

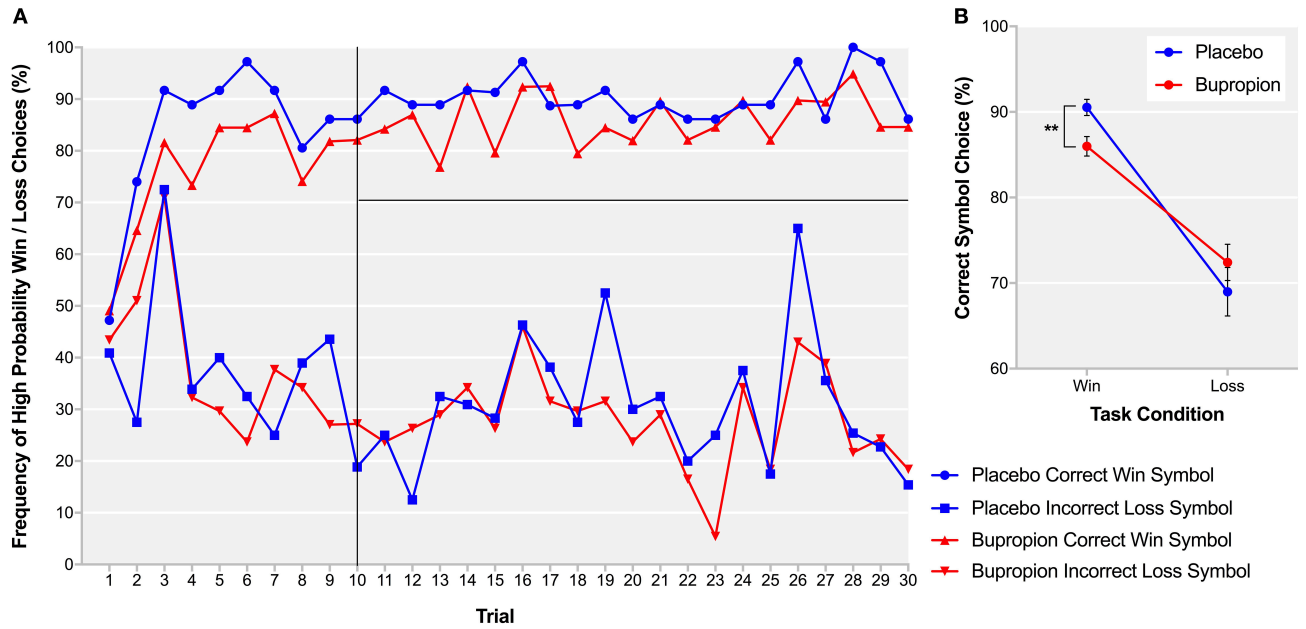

FIGURE 5 | (A) Learning curves for each treatment group depicting trial-by-trial the proportion of participants that chose the correct symbol in the win condition, associated with high-probability win (top lines) and the incorrect symbol in the loss condition, associated with high-probability loss (bottom lines) during the probabilistic instrumental learning task. **(B)** Proportion of participants choosing the correct symbol in the win and loss conditions averaged over the last 20 trials of the probabilistic instrumental learning task where learning had plateaued. Asterisks denote the degree of significance obtained for planned comparisons (**$p < 0.01$).

mechanism of action most commonly attributed to bupropion, the exact neuropharmacological actions of bupropion remain elusive, due to different actions *in vitro* vs. *in vivo* (36, 37). *In vitro*, bupropion is more potent at inhibiting dopamine than noradrenaline reuptake (IC_{50} of 2.0 and 5.0, respectively) (36) but the inhibition of dopamine reuptake itself is not particularly robust and was not thought to have pharmacological relevance (38). In contrast, *in vivo*, an acute dose of bupropion has been found to affect the firing rate of noradrenaline neurons in the locus coeruleus of the rat at doses more similar to those required for antidepressant-like activity in animal models (39, 40). It seems that the effects of bupropion on emotional processing may be mediated via noradrenaline and/or dopamine and further research is required in this area.

Reward Processing

It has previously been shown that administration of drugs with dopaminergic enhancing activity can improve performance on probabilistic instrumental learning tasks in healthy volunteers. For example, administration of L-DOPA, the metabolic precursor of dopamine, was found to significantly increase the likelihood of choosing the stimulus associated with high-probability win and subsequently the amount of money won during a probabilistic instrumental learning task, compared to the dopamine receptor antagonist haloperidol (19). Therefore, it could be expected that an acute dose of bupropion with dopaminergic enhancing activity would also improve performance on a probabilistic instrumental learning task in healthy volunteers; however, this was not found to be the case. Instead, bupropion reduced the likelihood of choosing the stimulus associated with high-probability win. Such a profile is similar to that seen in depression itself (16–18) and bupropion may therefore be predicted to worsen anhedonia at least early in treatment. However, care must be taken when interpreting these results obtained in a sample of healthy volunteers with regards to depression. Key differences in reward and emotional processing between healthy and depressed individuals are likely to have a large impact upon the effects of bupropion.

Indeed, in a healthy system with roof levels of dopamine, acute inhibition of the reuptake of dopamine could lead to a paradoxical decrease in cell firing via activation of the presynaptic autoreceptors (41). It has previously been shown, at least in rats, than an acute dose of bupropion induced an autoreceptor-mediated reduction in the firing of brain stem dopamine neurons (40, 42). Subsequent down-regulation of the autoreceptors may be required to reverse these effects, allow an increase in the levels of dopamine in the synapse and improve reward processing in healthy participants (43).

Bupropion could also differentially affect the phasic vs. tonic firing of dopamine neurons. Phasic firing refers to a transient burst of firing following presynaptic input in response to a stimulus and plays a crucial role in associative reward learning (44). Tonic firing refers to sustained firing at a constant frequency regulated by frontal activity in order to set the background level of dopamine and subsequently the responsivity of the dopaminergic system (44). Administration of bupropion may act to increase tonic levels of dopamine but as a result decrease the responsivity of the dopaminergic system such that phasic firing is actually reduced. This may reduce reward discriminability

such that the participant believes the neutral and win outcomes are of a similar magnitude (45). As such participants fail to or are slower to learn the association of a particular stimulus with high-probability win, thereby disrupting instrumental reward learning.

SSRIs have also been shown to reduce reward processing, for example, short-term treatment with the SSRI citalopram, but not the SNRI reboxetine, reduced ventral striatal, and ventral medial/orbitofrontal cortex activation in response to chocolate reward (13). However, more recent research suggests that longer-term treatment with SSRIs has a beneficial effect on reward processing, with 2 week citalopram treatment increasing reward learning and the effort applied to obtain rewards (46). Similarly, chronic administration of bupropion may be required for the beneficial effects on reward processing, in correspondence with the delay in the action of antidepressants to produce a clinical important therapeutic effect. Further research into the longer-term effects of bupropion on reward processing in MDD patients is required.

The bupropion group also displayed a slight increase in SHAPS score, and therefore, anhedonia, compared to placebo over time. The slight increase in anhedonia may be associated with acute adverse effects of bupropion on reward processing and may have clinical implications when starting treatment with bupropion. With the exception of the SHAPS, all of these effects occurred in the absence of any changes in subjective mood. This provides evidence that antidepressants acting on a range of neurotransmitters, including serotonin, noradrenaline and dopamine, all have early effects on the processing of affective stimuli prior to mood improvement. Our results therefore further support the neuropsychological theory of antidepressant action.

CONCLUSION

Despite its alternative mechanism of action involving dopamine, an acute dose of bupropion appears to have a similar profile of effects on emotional and reward processing to other antidepressants. Acute bupropion acts to restore the balance between negative and positive emotional processing but with adverse effects on reward processing and anhedonia, at least in healthy participants. The beneficial effects of bupropion on reward processing may only occur in MDD individuals or following repeated administration. As such, there is a dissociation of the acute effects of bupropion on positive emotional processing and reward processing in healthy volunteers indicating they may be different processes in the manifestation of the symptom clusters in MDD; however, the roles of different neurotransmitters, how they interact and their downstream effects needs to be unraveled. If the adverse effects of acute bupropion on reward processing are found to occur in MDD individuals, the use of bupropion to specifically target anhedonia should be monitored early in treatment for any initial worsening of anhedonic symptoms.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Central University Research Ethics Committee (CUREC, University of Oxford) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Central University Research Ethics Committee.

AUTHOR CONTRIBUTIONS

AW, RB, and NH recruited volunteers for this study and analyzed the data; CH, MB, and PC were involved in study and task design and oversaw the running and analysis of the study. AW drafted the first draft of the paper and all authors revised this draft.

FUNDING

This work was funded by the Medical Research Council (grant number: HQRWNT0) and supported by the NIHR Oxford Health Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. Preparation of the article was supported by funding awarded to AW by the NIHR Oxford Health Biomedical Research Centre. CH has received consultancy fees from P1vital, Servier, and Lundbeck. She is director of Oxford Psychologists Ltd. and holds shares in the same company. She has received grant income from Lundbeck, Servier, Sunovion, Johnson and Johnson and UCB. PC has received consultancy fees from Lundbeck. MB is employed part time by P1vital Ltd. and has received travel expenses from Lundbeck.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00482/full#supplementary-material

REFERENCES

1. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Ann Rev Clin Psychol.* (2005) 1:167–95. doi: 10.1146/annurev.clinpsy.1.102803.143916
2. Leppanen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr Opin Psychiatry* (2006) 19:34–9. doi: 10.1097/01.yco.0000191500.46411.00
3. Elliott R, Zahn R, Deakin JF, Anderson IM. Affective cognition and its disruption in mood disorders. *Neuropsychopharmacology* (2011) 36:153–82. doi: 10.1038/npp.2010.77
4. Roiser JP, Elliott R, Sahakian BJ. Cognitive mechanisms of treatment in depression. *Neuropsychopharmacology* (2012) 37:117–36. doi: 10.1038/npp.2011.183
5. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry* (2009) 195:102–8. doi: 10.1192/bjp.bp.108.051193
6. Pringle A, Browning M, Cowen PJ, Harmer CJ. A cognitive neuropsychological model of antidepressant drug action. *Prog Neuropsychopharmacol Biol Psychiatry* (2011) 35:1586–92. doi: 10.1016/j.pnpbp.2010.07.022

7. Harmer CJ, Cowen PJ. It's the way that you look at it'–a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc B Biol Sci.* (2013) 368:20120407. doi: 10.1098/rstb.2012.0407
8. Harmer CJ, Bhagwagar Z, Perrett DI, Vollm BA, Cowen PJ, Goodwin GM. Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology* (2003) 28:148–52. doi: 10.1038/sj.npp.1300004
9. Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *Am J Psychiatry* (2003) 160:990–2. doi: 10.1176/appi.ajp.160.5.990
10. Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry* (2004) 161:1256–63. doi: 10.1176/appi.ajp.161.7.1256
11. Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry* (2009) 166:1178–84. doi: 10.1176/appi.ajp.2009.09020149
12. Nutt D, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, et al. The other face of depression, reduced positive affect: the role of catecholamines in causation and cure. *J Psychopharmacology* (2007) 21:461–71. doi: 10.1177/0269881106069938
13. McCabe C, Mishor Z, Cowen PJ, Harmer CJ. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biol Psychiatry* (2010) 67:439–45. doi: 10.1016/j.biopsych.2009.11.001
14. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science* (1997) 275:1593–9. doi: 10.1126/science.275.5306.1593
15. Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci.* (2005) 8:1481–9. doi: 10.1038/nn1579
16. Henriques JB, Davidson RJ. Decreased responsiveness to reward in depression. *Cogn Emot.* (2000) 14:711–24. doi: 10.1080/026999300501176841
17. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res.* (2008) 43:76–87. doi: 10.1016/j.jpsychires.2008.03.001
18. Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, et al. Reduced reward learning predicts outcome in major depressive disorder. *Biol Psychiatry* (2013) 73:639–45. doi: 10.1016/j.biopsych.2012.10.014
19. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* (2006) 442:1042–5. doi: 10.1038/nature05051
20. Kranz GS, Kasper S, Lanzenberger R. Reward and the serotonergic system. *Neuroscience* (2010) 166:1023–35. doi: 10.1016/j.neuroscience.2010.01.036
21. First MB. *User's Guide for the Structured Clinical Interview for DSM-IV Axis 1 Disorders: SCID-I Clinician Version*. Washington, DC: American Psychiatric Press (1997).
22. Nelson HE, Willison J. National adult reading test (NART). 2nd ed, Hazel, E. Nelson with Jonathan Willison. 1991, NFER-Nelson. *Int J Geriatr Psychiatry Banner* (1991) 7:533. doi: 10.1002/gps.930070713
23. Huneke NT, Walsh AE, Brown R, Browning M, Harmer C. No evidence for an acute placebo effect on emotional processing in healthy volunteers. *J Psychopharmacol.* (2017) 31:1578–87. doi: 10.1177/0269881117739552
24. Jefferson JW, Pradko JF, Muir KT. Bupropion for major depressive disorder: Pharmacokinetic and formulation considerations. *Clin Ther.* (2005) 27:1685–95. doi: 10.1016/j.clinthera.2005.11.011
25. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23:56–62. doi: 10.1136/jnnp.23.1.56
26. Eysenck HJ. *Manual of the Eysenck Personality Questionnaire (Junior and Adult)*. London, UK: Hodder and Stoughton (1975).
27. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol.* (1988) 54:1063–70. doi: 10.1037/0022-3514.54.6.1063
28. Von Zerssen D, Petermann F. *Bf-SR – The Befindlichkeits Scale – Revised*. Göttingen: Hogrefe (2011).
29. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry* (1995) 167:99–103. doi: 10.1192/bjp.167.1.99
30. Walsh AEL, Browning M, Drevets WC, Furey M, Harmer CJ. Dissociable temporal effects of bupropion on behavioural measures of emotional and reward processing in depression. *Philos Trans R Soc Lond B Biol Sci.* (2018) 373:20170030. doi: 10.1098/rstb.2017.0030
31. Harrison NA, Voon V, Cercignani M, Cooper EA, Pessiglione M, Critchley HD. A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. *Biol Psychiatry* (2016) 80:73–81. doi: 10.1016/j.biopsych.2015.07.018
32. Grillon C, Levenson J, Pine DS. A single dose of the selective serotonin reuptake inhibitor citalopram exacerbates anxiety in humans: a fear-potentiated startle study. *Neuropsychopharmacology* (2007) 32:225–231. doi: 10.1038/sj.npp.1301204
33. Browning M, Reid C, Cowen PJ, Goodwin GM, Harmer CJ. A single dose of citalopram increases fear recognition in healthy subjects. *J Psychopharmacol.* (2007) 21:684–90. doi: 10.1177/0269881106074062
34. Linner L, Endersz H, Ohman D, Bengtsson F, Schalling M, Svensson TH. Reboxetine modulates the firing pattern of dopamine cells in the ventral tegmental area and selectively increases dopamine availability in the prefrontal cortex. *J Pharmacol Exp Ther.* (2001) 297:540–6.
35. Page ME, Lucki I. Effects of acute and chronic reboxetine treatment on stress-induced monoamine efflux in the rat frontal cortex. *Neuropsychopharmacology* (2002) 27:237–47. doi: 10.1016/S0893-133X(02)00301-9
36. Horst WD, Preskorn SH. Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion. *J Affect Disord.* (1998) 51:237–54. doi: 10.1016/S0165-0327(98)00222-5
37. Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, Learned-Coughlin S. A review of the neuropharmacology of bupropion, a dual norepinephrine and dopamine reuptake inhibtor. *Prim Care Companion J Clin Psychiatry* (2004) 6:159–66. doi: 10.4088/PCC.v06n0403
38. Ferris RM, Cooper BR, Maxwell RA. Studies of bupropion's mechanism of antidepressant activity. *J Clin Psychiatry* (1983) 44(Pt 2):74–8.
39. Cooper BR, Wang CM, Cox RF, Norton R, Shea V, Ferris RM. Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin[reg]) are mediated by a noradrenergic mechanism. *Neuropsychopharmacology* (1994) 11:133–41. doi: 10.1038/npp.1994.43
40. Ascher JA, Cole JO, Colin JN, Feighner JP, Ferris RM, Fibiger HC, et al. Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry* (1995) 56:395–401.
41. Ford CP. The role of D2-autoreceptors in regulating dopamine neuron activity and transmission *Neuroscience* (2014) 282:13–22. doi: 10.1016/j.neuroscience.2014.01.025
42. Ferris RM, Cooper BR. Mechanism of antidepressant activity of bupropion. *J Clinical Psychiatry Monogr Seri.* (1993) 11:2–14.
43. Frazer A, Benmansour S. Delayed pharmacological effects of antidepressants. *Mol Psychiatry* (2002) 7:S23–8. doi: 10.1038/sj.mp.4001015
44. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* (1991) 41:1–24. doi: 10.1016/0306-4522(91)90196-U
45. Rutledge RB, Skandali N, Dayan P, Dolan RJ. Dopaminergic modulation of decision making and subjective well-being. *J Neurosci.* (2015) 35, 9811–22. doi: 10.1523/JNEUROSCI.0702-15.2015
46. Scholl J, Kolling N, Nelissen N, Browning M, Rushworth MF, Harmer CJ. Beyond negative valence: 2-week administration of a serotonergic antidepressant enhances both reward and effort learning signals. *PLoS Biol.* (2017) 15:e2000756. doi: 10.1371/journal.pbio.2000756

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 21 November 2018
doi: 10.3389/fpsyt.2018.00615

Moral Emotions and Social Economic Games in Paranoia

George Savulich[1,2]*, *Hannah Jeanes*[3], *Nicole Rossides*[3], *Sahaj Kaur*[3], *Alice Zacharia*[3], *Trevor W. Robbins*[3] *and Barbara J. Sahakian*[1,2]

[1] Department of Psychiatry, University of Cambridge, School of Clinical Medicine, Cambridge, United Kingdom, [2] Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, United Kingdom, [3] Department of Psychology, University of Cambridge, Cambridge, United Kingdom

Impaired social cognitive processes are putative psychological mechanisms implicated in the formation and maintenance of paranoid beliefs. Paranoia denotes unfounded fears about the hostile intentions of others and is prevalent in a significant proportion of the general population. We investigated social cognition in healthy participants selectively recruited to have a broad occurrence of paranoid thinking (n = 89). Participants completed a novel computerized task of moral emotions and two social economic exchange games (Prisoner's Dilemma, Ultimatum Game) from the EMOTICOM neuropsychological test battery. Regression analyses revealed that delusional ideation predicted shameful feelings when the victim of deliberate harm by another person. Cooperative behavior on the Prisoner's Dilemma was greatest when the participant and opponent contributed equally to joint earnings. Participants demonstrated significantly more punishment behavior when contributions were unequal and stole more from the opponent using a suspicious strategy of gameplay. In addition, paranoid thinking was positively associated with more stealing from the cooperative opponent. On the Ultimatum Game, participants accepted significantly more unequal offers when the opponent contributed more and sensitivity to fairness was greatest when the participant contributed more. These data demonstrate that delusional ideation predicts a maladaptive emotional response to interpersonal harm and that paranoid thinking may lead to reduced cooperation toward mutual reward. The effects of paranoia on moral emotions and pro-social behavior at more severe levels of persecutory thinking warrant further investigation.

Keywords: paranoia, social cognition, moral emotions, economic games, delusions

OPEN ACCESS

Edited by:
Allan Young,
King's College London,
United Kingdom

Reviewed by:
Giancarlo Dimaggio,
Centro di Terapia Metacognitiva Interpersonale (CTMI), Italy
Rebecca Strawbridge,
King's College London,
United Kingdom

***Correspondence:**
George Savulich
gjs46@medschl.cam.ac.uk

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *18 April 2018*
Accepted: *01 November 2018*
Published: *21 November 2018*

Citation:
Savulich G, Jeanes H, Rossides N, Kaur S, Zacharia A, Robbins TW and Sahakian BJ (2018) Moral Emotions and Social Economic Games in Paranoia. Front. Psychiatry 9:615. doi: 10.3389/fpsyt.2018.00615

INTRODUCTION

Impaired social cognition is a key feature of schizophrenia, with deficits typically found in emotion identification, experience sharing and emotional responding (1). These impairments are one pathway to a first episode of psychosis (2) and strongly predict functional and social outcomes in psychotic disorders [(3, 4)]. In patients with schizophrenia, impaired social cognitive processes have shown to account for a larger proportion of the variance in community functioning than non-social cognitive impairments (5). Social cognitive impairments have also shown to lead to more difficulty inferring the mental states of others, including their beliefs and intentions (1, 6).

Paranoia is characterized by unfounded fears about the harmful intentions of others (7). Social cognition is highly relevant to paranoid thinking, as hostile perceptions during social interactions are likely to precipitate threat beliefs and related distress. Paranoid thinking is symptomatic of psychosis and also prevalent in 10–15% of the general population (8). Paranoia is associated with several cognitive and affective processes implicated in the formation and maintenance of a persecutory delusion (9, 10). "Jumping to conclusions" (JTC) is a reliably established probabilistic reasoning bias whereby deluded patients use less information to make a decision compared with healthy controls [e.g., (11)]. Individuals with non-clinical paranoia have also shown evidence of cognitive biases similar to those with persecutory delusions. For example, healthy individuals with elevated trait paranoia have shown to interpret emotionally ambiguous information in a paranoid manner (12), an effect that matched symptoms in patients with psychosis (13). Studies of non-clinical paranoid experiences are therefore important to inform our understanding of those presenting clinically.

Studies of social cognition in schizophrenia have primarily focused on impairments in emotion perception, theory of mind and attributional style (1, 14). Deficits in theory of mind and heightened social anxiety have shown to make independent contributions to the development of paranoia, thus raising the possibility of distinct cognitive and emotional pathways (15). Social anxiety is also related to negative symptoms and self-stigma in schizophrenia, often leading to expectation of embarrassment or rejection (15, 16). It has been proposed that persecutory delusions are triggered by interpersonal stress leading to complex interactions between reduced mentalizing abilities, a vulnerable self-concept and over-activation of the threat/protection system (17). Paranoia is then reinforced by cognitive biases supporting inflexible beliefs about being at risk of harm by others (e.g., JTC; interpretation bias; bias against disconfimatory information) [see (18) for a review]. Studies of attributional bias have further shown that patients with persecutory delusions make externalizing attributions for negative events by blaming others, which serves to protect the self (19–21). However, these studies typically use questionnaire measures that present hypothetical positive/negative situations without measuring emotional responses or differentiating the intention of the agent of action. We thus used a novel "Moral Emotions" task to investigate emotional responses when both the *victim* and *victimiser* of *accidental* (unintentional) and *deliberate* (intentional) harm in cartoon scenarios depicting interpersonal behavior (22). Guilt and shame are two moral emotions associated with a range of psychological disorders (23). Guilt develops in recognition of oneself as an agent of a negative outcome for another person, whereas shame reflects an emotional appraisal of oneself as personally inadequate, usually following judgement, criticism, or humiliation by others (24). Shame increases paranoia following a stressful life event (25) and is associated with anxiety-related processes in the general population (26). Moral emotions are therefore likely to be compromised in healthy individuals with high levels of paranoia and predicted by variation in different traits (e.g., paranoia, anxiety) depending on the intention of another person when harmed.

Social decision-making is another cognitive process influenced by the inferred knowledge and intentions of others (27, 28). Economic exchange games, such as the "Prisoner's Dilemma" (29) and "Ultimatum Game" (30), are established interactive paradigms for assessing cooperation, sensitivity to fairness and the tendency to inflict punishment. These games involve choosing to split sums of money based on the player's contribution, the opponent's behavior and the amount proposed. Paranoia has shown an association with distrust-based behavior (expecting a competitive opponent), but not greed-based behavior (exploiting a cooperative opponent), when playing the Prisoner's Dilemma (31). Paranoia has also shown an association with more attributions of harmful intent for both fair and unfair dictators on the "Dictator Game" (32). When playing the Ultimatum Game, healthy participants consistently forfeit their own gains when offers are deemed considerably unfair [e.g., below 30%; (33)], which is thought to reflect heightened sensitivity to fairness (34) or a desire to punish socially unacceptable behavior (35). Patients with schizophrenia are less strategic and have shown to accept more unfair offers and reject more fair offers compared with healthy controls (36). However, others have found higher rejection of unfair compared with fair offers in patients with schizophrenia (37, 38) as well as no significant differences in acceptance rates compared with controls (39). It is possible that behavioral performance is motivated by distrust about the opponent's intentions (i.e., predicting that the opponent will always defect, despite minimizing mutual outcomes), but that sensitivity to fairness remains relatively intact or relates to the severity of symptoms in schizophrenia (for example, is impaired in those with negative symptoms).

We investigated social cognition in the general population reporting a broad occurrence of paranoid thinking. Specifically, we examined the role of paranoia and other traits relevant to psychosis on moral emotional processing and social decision-making, two processes requiring the ability to infer the mental states of others. As paranoia denotes fears about the harmful intentions of others (7), we expected that high levels of paranoia would alter both emotional and cognitive processing during three tasks involving the perception of other's intentions toward the self. Tasks were selected from EMOTICOM (22), a novel neuropsychological test battery for assessing affective domains. On the basis of models indicating a weakened sense of self in those with paranoia [e.g., (17)], we firstly hypothesized that paranoid thinking would predict shameful feelings when the victim of intentional (but not unintentional) harm by another person on the Moral Emotions task. Secondly, we hypothesized that in line with previous research [e.g., (31)], distrust-based punishment behavior would be greatest when playing against a suspicious opponent on the Prisoner's Dilemma, and that choice to compete (stealing) would be associated with paranoid thinking. Finally, we hypothesized that acceptance rates would increase as offers became increasingly fair on the Ultimatum Game, consistent with preserved sensitivity to fairness [e.g., (37, 39)].

MATERIALS AND METHODS

Participants

Eighty-nine participants were recruited from internal mailing of a volunteer panel at the University of Cambridge and advertisements in the local Cambridgeshire area. Inclusion criteria were fluency in English; not currently taking any psychiatric medication or receiving psychological treatment; and not having a current or past psychiatric diagnosis. All participants were screened on these criteria using the Mini-International Neuropsychiatric Interview (40). Participants were selectively recruited to have a wide range of scores of the Green Paranoid Thoughts Scale [GPTS; (41)] to capture naturally occurring paranoid thinking in the general population. In order to reduce multicollinearity between predictor variables potentially entered in regression analyses (up to seven trait measures, see below), a sample size of at least 80 was determined to ensure that there were at least 10 times as many observations from the sample.

Questionnaire Measures

The National Adult Reading test [NART; (42)] is a 50-item estimate of premorbid intelligence. Participants are instructed to read aloud 50 words of atypical phonemic pronunciation. Higher scores (0–50) indicate more correct responses (i.e., higher intelligence).

The Green Paranoid Thoughts Scale [GPTS; (41)] is a 32-item multidimensional measure of paranoid thinking including thoughts of persecution and ideas of reference. Participants indicate thoughts that they might have had about others in the last month using a 5-point Likert scale (1 = not at all to 5 = totally). Higher scores (0–160) indicate more paranoid thinking.

The Paranoia Scale [PS; (43)] is a 20-item measure of trait paranoia. Participants indicate thoughts about themselves and others using a 5-point Likert scale (1 = not at all to 5 = totally). Higher scores (0–100) indicate more trait paranoia.

Peters' Delusions Inventory [PDI-21; (44)] is a 21-item multidimensional measure of delusional ideation (including beliefs and vivid mental experiences). Participants first circle "yes/no" questions about experiences they might have had. For "yes" answers, participants rate how distressing, preoccupying, and true they believe each experience to be using 5-point Likert scales (1 = not at all distressing to 5 = very distressing; 1 = hardly ever think about it to 5 = think about it all the time; 1 = don't believe it's true to 5 = believe it is absolutely true). Higher scores (0–336) indicate more delusional ideation.

The Cardiff Anomalous Perceptions Scale [CAPS; (45)] is a 32-item measure of anomalous perceptions. Participants answer "yes/no" questions about sensations and perceptions that they may have experienced. Higher scores (0–32) indicate more anomalous perceptions.

The Spielberger Trait Anxiety Scale [STAI-State; (46)] is a 20-item of trait anxiety. Participants rate statements in relation to how they usually feel using a 4-point Likert scale (1 = not at all to 4 = very much so). Higher scores (0–80) indicate more trait anxiety.

The Beck Depression Inventory [BDI-II; (47)] is a 21-item of depression. Participants read statements and circle answers corresponding with how they have been feeling in the past 2 weeks. Higher scores (0–63) indicate more depression.

The Cognitive Flexibility Scale [CF; (48)] is a 12-item measure of cognitive flexibility (i.e., awareness of situational alternatives). Participants rate statements about their beliefs, feelings, and behaviors using a 6-point Likert scale (1 = I strongly disagree to 6 = I strongly agree). Higher scores (0–72) indicate more cognitive flexibility.

EMOTICOM Measures

Moral Emotions Task

The Moral Emotions task measures moral responses to intentional and unintentional harmful actions by another person (22). Participants were presented with moral scenarios using cartoons. Half of the scenarios depict deliberate harm by another person (**Figure 1A**), whereas the other half depicts accidental harm by another person (**Figure 1B**) (both leading to a negative outcome). Participants were asked to rate how much shame and guilt that they have in each scenario as both the victimiser (the person who commits the action) and victim (the person who experiences the consequences). Higher average ratings indicate more shame and guilt.

Prisoner's Dilemma

The Prisoner's Dilemma assesses cooperation with an opponent (29). Participants were first asked to compete with an avatar by pressing the space bar, as quickly as possible, to fill a jar with coins. Each trial is manipulated so that the participant wins more coins, the opponent wins more coins or both the participant and the opponent win the same amount of coins. Earnings are then combined and the participant is instructed to either split or steal the total sum. Participants are told that if they (the participant and the opponent) both split, then they each get half the money, and if they both steal, then they each get nothing (**Figure 2**). However, if the participant steals and the opponent splits, then the participant gets the total earnings and the opponent gets nothing. Participants face three different opponent strategies throughout the game: suspicious (tit for tat, but starts with steal), tit for two tats (starts with split, then changes behavior after the player steals two times consecutively) and cooperative (always splits).

Ultimatum Game

The Ultimatum Game (30) assesses fairness sensitivity and the tendency to inflict punishment following an unfair offer. Participants and an avatar first earn money by independently uncovering three out of nine yellow ovals; ovals that turn black reveal £3 and ovals that turn red earn nothing. Similar to Prisoner's Dilemma, each trial is manipulated so that the participant wins more money, the opponent wins more money or both the participant and the opponent win the same amount of money. Earnings are then combined and the participant is told whether or not they or the opponent will decide how the total sum is split. If the opponent decides, then the participant gets the choice either to accept or reject their offer (**Figure 2**). Offers

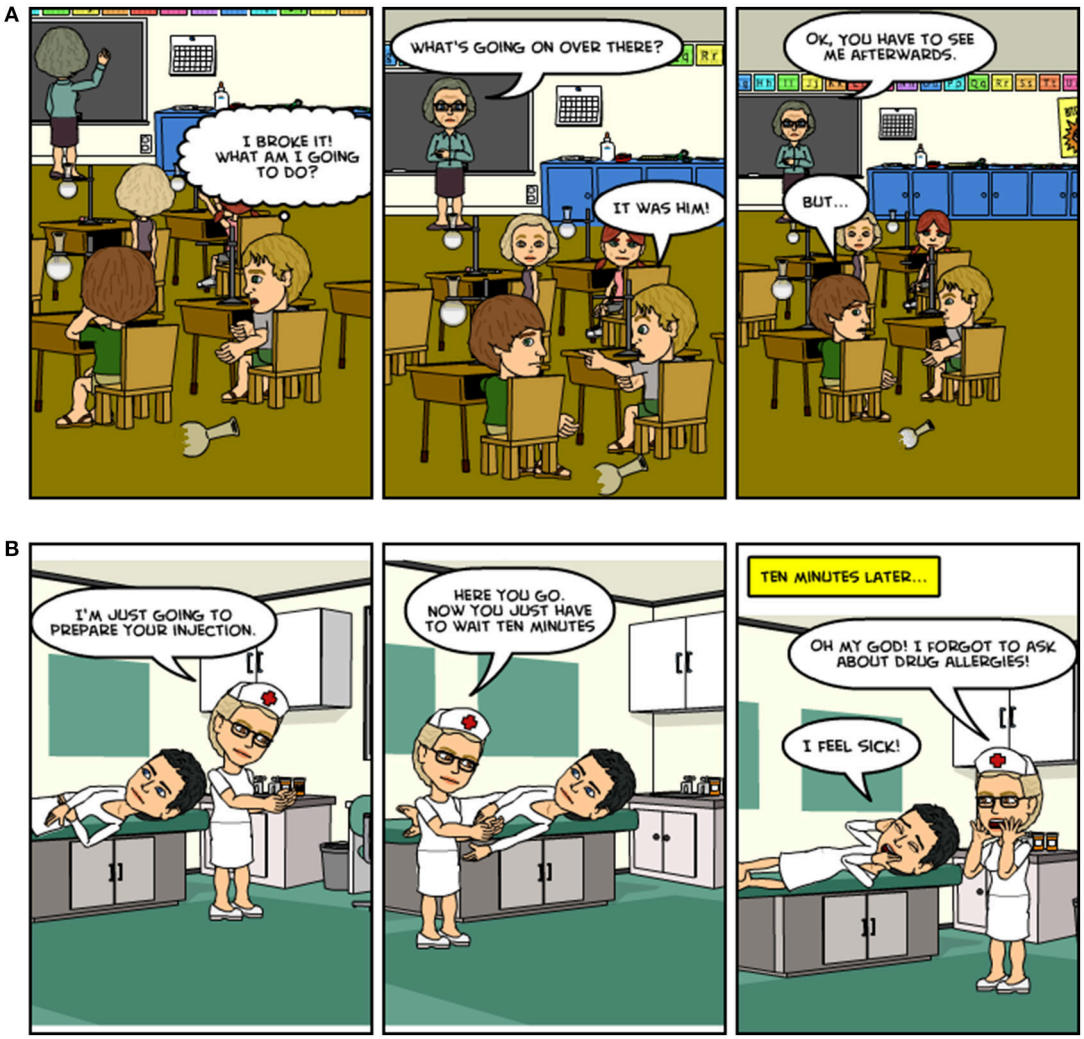

FIGURE 1 | (A) An example of a scene from the EMOTICOM Moral Emotions task depicting both the victim and victimiser of deliberate harm**. (B)** An example of a scene from the EMOTICOM Moral Emotions task depicting both the victim and victimiser of accidental harm.

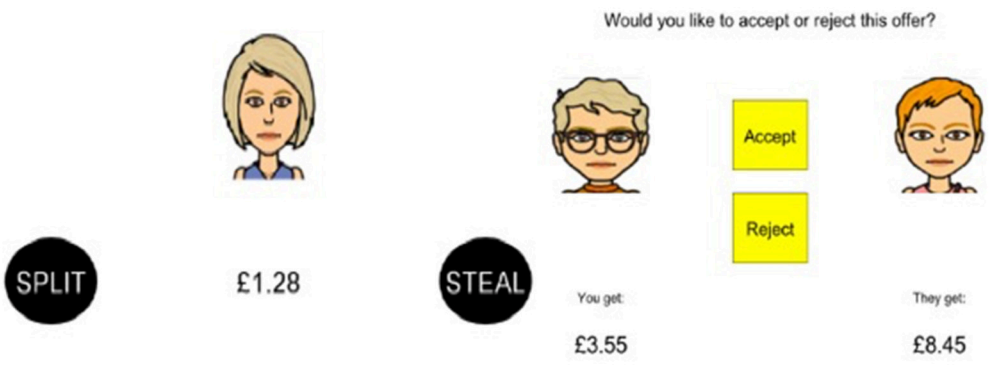

FIGURE 2 | Examples of offers from the Prisoner's Dilemma (left) and Ultimatum Game (right).

have seven levels of fairness ranging from very fair (50:50%) to increasingly unfair (10:90%). If the participant accepts, then they each get the allotted amount, and if they reject, then they both get nothing.

Procedure

This study received full ethical approval from the University of Cambridge Psychology Research Ethics committee (reference: Pre.2015.046). Participants meeting inclusion criteria (after telephone screening) were invited to attend a single session at the University of Cambridge Behavioral and Clinical Neuroscience Institute. Participants first provided written informed consent, followed by basic demographic information and an estimate of premorbid intelligence. Participants then completed EMOTICOM measures using a touch screen laptop (Dell XT3) in a counterbalanced order using a Latin-square design. The EMOTICOM task battery was delivered using PsychoPy. Participants then completed the questionnaire measures; questionnaires were always administered after the tasks to reduce paranoia-related demand characteristics. Participants were thanked and paid for their time.

RESULTS

Participant Characteristics

Participant characteristics for the whole sample ($n = 89$) are presented in **Table 1**. The mean GPTS score was similar to those previously reported in other samples from the general population recruited using this scale, $M = 53.57$, $SD = 19.91$, range = 32–111 (12, 41).

Moral Emotions Task

Regression Analyses

Personality trait measures were first correlated with moral emotions. Only variables with more than one significant association were entered as predictor variables in a hierarchical multiple regression analysis, with paranoia and psychosis measures entered into Block 1 and anxiety, depression, and cognitive flexibility measures entered into Block 2. This order of entry controls for highly correlated and conceptually similar variables (e.g., anxiety; Block 2) without corrupting the predictors of *a priori* interest (e.g., paranoid thinking; Block 1) (49).

TABLE 1 | Demographic and trait measures for the whole sample (means and standard deviations).

	$n = 89$
DEMOGRAPHIC MEASURES	
Age (years)	22.29 (±5.22)
Gender (male: female)	35 M: 54 F
Intelligence (NART)	110.72 (±9.44)
TRAIT MEASURES	
Paranoid thinking (GPTS)	53.57 (±19.91)
Paranoia (PS)	39.18 (±11.01)
Delusional ideation (PDI)	39.92 (±28.19)
Anomalous perceptions (CAPS)	4.62 (±4.34)
Anxiety (STAI-Trait)	10.01 (±3.53)
Depression (BDI-II)	6.11 (±5.65)
Cognitive flexibility (CF)	56.96 (±6.28)

NART, National Adult Reading Test; GPTS, Green Paranoid Thoughts Scale; PS, Paranoia Scale; PDI, Peters' Delusions Inventory; CAPS, Cardiff Perceptions Inventory; STAI-Trait, Spielberger Trait Anxiety Inventory; BDI-II, Beck Depression Inventory; CF, Cognitive Flexibility Scale.

Victimiser of Harm (Deliberate and Accidental)

Moral emotions were not significantly associated with any trait measure when the victimiser of deliberate or accidental harm (all p's > 0.07). Average ratings for these conditions were therefore not modeled using regression analyses.

Victim of Deliberate Harm

The average rating of shame when the victim of deliberate harm was significantly associated with the GPTS ($r = 0.32$, $p = 0.002$), PS ($r = 0.32$, $p = 0.002$), PDI ($r = 0.42$, $p < 0.001$), CAPS ($r = 0.22$, $p = 0.04$), CF ($r = -0.22$, $p = 0.04$), and BDI-II ($r = 0.34$, $p = 0.001$); the average rating of guilt when the victim of deliberate harm was significantly associated with the GPTS ($r = 0.25$, $p = 0.02$), PS ($r = 0.28$, $p = 0.008$), CAPS ($r = 0.26$, $p = 0.02$), CF ($r = -0.26$, $p = 0.01$), and BDI-II ($r = 0.37$, $p < 0.001$). These measures were entered as predictor variables in subsequent regression analyses.

Regression analyses are presented in **Table 2**. **Shame:** The first model (Model 1; paranoia/psychosis measures) accounted for 45% of the variance in shameful feelings and was significant, $F_{(4, 84)} = 5.21$, $p = 0.001$. Delusional ideation significantly predicted shame[1], $\beta = 0.35$, $t = 2.62$, $p = 0.01$. The final model (Model 2; now including cognitive flexibility and depression) accounted for 46% of the variance in shameful feelings and was also significant, $F_{(6, 82)} = 3.72$, $p = 0.003$. Delusional ideation again predicted shame, $\beta = 0.31$, $t = 2.35$, $p = 0.02$. **Guilt:** Model 1 (paranoia/psychosis measures) accounted for 32% of the variance in guilty feelings and was significant, $F_{(3, 85)} = 3.42$, $p = 0.02$. However, no variable made an independent contribution. The final model (now including cognitive flexibility and depression) accounted for 41% of the variance and was also significant, $F_{(5, 83)} = 3.26$, $p = 0.01$. No variable made an independent contribution.

Victim of Accidental Harm

Shame: The average rating of shame when the victim of accidental harm was significantly associated with the GPTS ($r = 0.24$, $p = 0.04$) and CAPS ($r = 0.22$, $p = 0.04$). The model was significant, $F_{(2,86)} = 3.75$, $p = 0.03$ and accounted for 28% of the variance. However, neither variable made independent contributions. **Guilt:** The average rating of guilt when the victim of accidental harm was significantly associated with the GPTS ($r = 0.29$, $p = 0.007$), PS ($r = 0.22$, $p = 0.04$), and BDI ($r = 0.28$, $p = 0.006$). Regression analyses revealed that both models were significant [Model 1: $F_{(2, 86)} = 3.89$, $p = 0.02$ and Model 2: $F_{(3, 85)} = 3.68$, $p = 0.02$], accounting for 28% and 33% of

[1]Correlational analyses revealed that mean scores on the PDI and GPTS were significantly associated, $r = 0.45$, $p < 0.001$. Scores on the PDI ranged from 0 – 135.

TABLE 2 | Hierarchical multiple regression analyses entering shameful feelings when the victim of deliberate harm as the dependent variable (Moral Emotions task).

Model	Predictor	β	*t*	*p*	95% CI	Partial correlation	R-Squared
1 Shame (Victim of deliberate harm)	GPTS	0.17	1.33	0.19	−0.004, 0.02	0.14	
	PS	−0.02	−0.14	0.89	−0.03, 0.02	−0.02	
	PDI	**0.35**	**2.62**	**0.01**	**0.003, 0.02**	**0.28**	0.45
	CAPS	0.02	0.15	0.88	−0.05, 0.05	0.02	
2 Shame (Victim of deliberate harm)	GPTS	0.15	1.15	0.25	−0.01, 0.02	0.13	
	PS	−0.07	−0.46	0.65	−0.03, 0.02	−0.05	
	PDI	**0.32**	**2.35**	**0.02**	**.002, 0.02**	**0.25**	0.46
	CAPS	−0.02	−0.15	0.64	−0.06, 0.05	−0.02	
	CF	−0.05	−0.47	0.64	−0.04, 0.03	−0.05	
	BDI	0.14	1.07	0.29	−0.02, 0.07	0.12	

GPTS, Green Paranoid Thoughts Scale; PS, Paranoia Scale; PDI, Peters' Delusions Inventory; CAPS, Cardiff Perceptions Inventory; CF, Cognitive Flexibility Scale; BDI-II, Beck Depression Inventory. Bold indicates a significant predictor.

the variance, respectively. Again, no variables made independent contributions.

Prisoner's Dilemma

The percentage of steals was calculated as the number of trials that the participant chose to steal from their opponent from the total number of trials across each strategy type. The Contribution (Participant contributed more, Opponent contributed more, Equal contributions) × Strategy (Suspicious, Tit for two tats, Cooperative) interaction was not significant, $F_{(4, 84)} = 0.22$, $p = 0.93$. However, there was a main effect of Contribution, $F_{(2, 86)} = 8.15$, $p = 0.001$, partial $\eta^2 = 0.16$ (Participant contributed more: $M = 36.95\%$, $SD = 0.33$; Opponent contributed more: 36.97%; $SD = 0.33$; Equal contributions: $M = 30.43\%$, $SD = 0.30$; **Figure 3**), such that the percentage of steals was significantly less when the participant and opponent contributed equally [Equal contributions vs. Participant, $t_{(87)} = 3.65$, $p < 0.001$; Equal contributions vs. Opponent, $t_{(87)} = 3.02$, $p = 0.003$]. The percentage of steals between the participant and opponent contributions was not significant ($p = 0.99$).

There was also a main effect of Strategy, $F_{(4, 84)} = 6.90$, $p = 0.002$, partial $\eta^2 = 0.14$ (Suspicious player: $M = 40.96\%$, $SD = 0.33$; Tit for two tats player: $M = 32.07\%$, $SD = 0.37$; Cooperative player: $M = 31.19\%$, $SD = 0.34$; **Figure 3**), such that the highest percentage of steals was taken from the suspicious opponent [Cooperative vs. Suspicious, $t_{(88)} = 2.58$, $p = 0.001$; Tit for two tats vs. Suspicious, $t_{(87)} = 3.73$, $p < 0.001$]. The percentage of steals between the cooperative and tit for two tat strategies was not significant ($p = 0.66$; **Figure 3**).

Correlational analyses revealed that the percentage of steals made when the opponent cooperated was positively associated with paranoid thinking (GPTS; $r = 0.22$, $p = 0.04$).

Ultimatum Game

A repeated-measures ANOVA with the factors Contribution (Participant contributed more, Opponent contributed more, Equal contributions) and Offer (10, 20, 25, 30, 35, 40, and 50%) for acceptance rates revealed a significant interaction, $F_{(12, 77)} = 105.76$, $p < 0.001$, partial $\eta^2 = 0.94$. There was a main effect of Contribution, $F_{(2, 87)} = 50.78$, $p < 0.001$, partial $\eta^2 = 0.54$ (Opponent contributed more: $M = 69.02\%$, $SD = 0.23$; Participant contributed more: $M = 54.01\%$, $SD = 0.31$; Equal contributions: $M = 52.21\%$, $SD = 0.27$), such that the percentage of acceptance was highest when the opponent contributed more [Opponent vs. Participant, $t_{(88)} = 7.14$, $p < 0.001$; Opponent vs. Equal contribution, $t_{(88)} = 9.84$, $p < 0.001$]. The percentages of acceptance between the participant's contribution and equal contributions were not significantly different ($p = 0.11$).

As expected, there was also a main effect of Offer, $F_{(6, 83)} = 63.53$, $p < 0.001$, partial $\eta^2 = 0.82$, with the percentage of acceptance increasing monotonically as the offer increased (i.e., became more fair: 50%: $M = 98.88\%$, $SD = 0.06$; 40%: $M = 81.27\%$, $SD = 0.26$; 35%: $M = 60.21\%$, $SD = 0.27$; 30%: $M = 58.24\%$, $SD = 0.35$; 25%: $M = 44.76\%$, $SD = 0.39$; 20%: $M = 38.20\%$, $SD = 0.39$; 10%: $M = 27.34\%$, $SD = 0.43$; **Figure 4**). All adjacent conditions (with the exception of 65% to 75%) significantly differed from each other (all p's < 0.001).

To interpret the Contribution x Offer interaction, offer sensitivity was calculated as a measure of the degree to which participants increased their inclination to accept the offer as the amount proposed by the avatar increased. Offer sensitivity was calculated for each Contribution type using the following formula: *Offer sensitivity* = [2*acceptance at 50% offer] + [1*acceptance at 40% offer] + [0*acceptance at 30% offer]–[1*acceptance at 20% offer]–[2*acceptance at 10% offer]/Average offer. There was a main effect of Contribution, $F_{(2, 85)} = 15.74$, $p < 0.001$, partial $\eta^2 = 0.27$. Sensitivity to fairness was greatest when the participant contributed more (Participant contributed more: $M = 5.78$, $SD = 4.13$; Opponent contributed more: $M = 3.81$, $SD = 2.19$; Equal contributions: $M = 5.00$, $SD = 3.52$; **Figure 4**), which significantly differed from when the opponent contributed more, $t_{(86)} = 5.69$, $p < 0.001$ and when equal contributions were made, $t_{(86)} = 2.81$, $p = 0.006$. Offer sensitivities between the opponent contribution and equal contributions were also significantly different, $t_{(88)} = 4.27$, $p < 0.001$.

Correlational analyses revealed that the overall average percentage of steals on the Prisoner's Dilemma ($M = 34.72\%$, $SD = 0.26$) was negatively associated with the overall average percentage of offers accepted on the Ultimatum Game across conditions ($M = 58.41\%$, $SD = 0.26$), $r = -0.26$, $p = 0.02$.

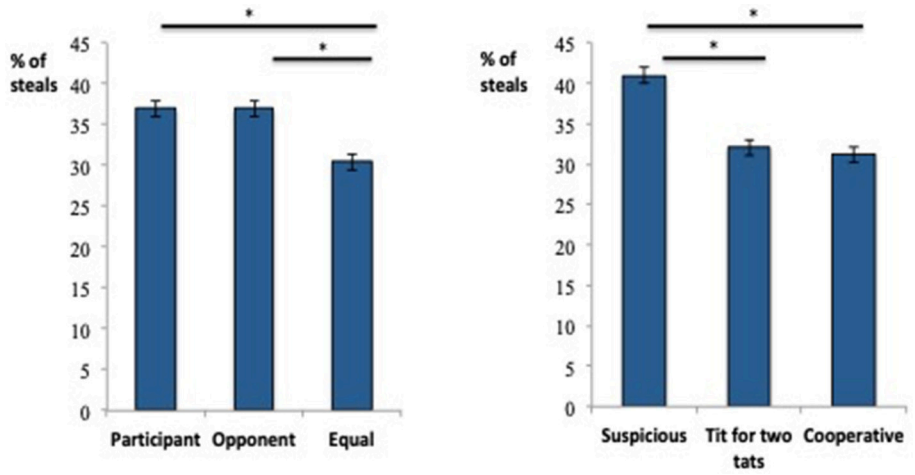

FIGURE 3 | Main effects of Contribution type (left) and Player Strategy (right) on the Prisoner's Dilemma. *Indicates a significant difference between means.

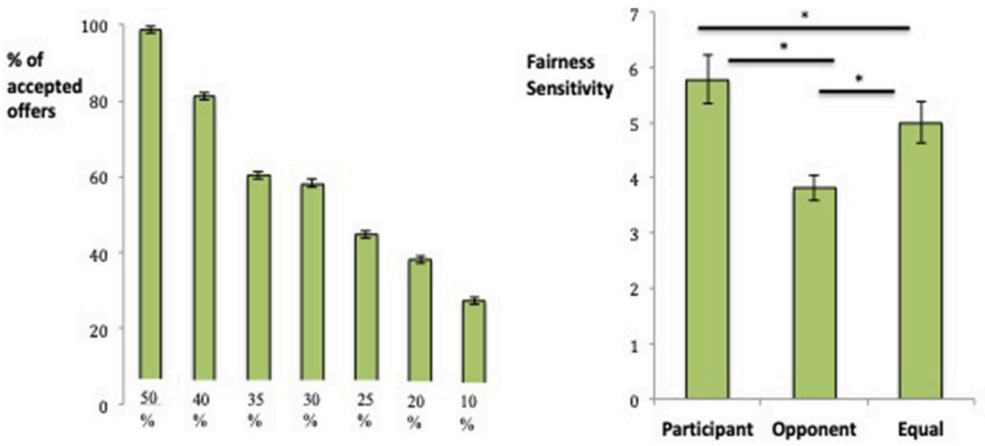

FIGURE 4 | Main effect of Offer at each level of fairness (left) and fairness sensitivity for each Contribution type (right) on the Ultimatum Game. *Indicates a significant difference between means.

DISCUSSION

We used a single-trait approach to investigate the effects of paranoia on moral emotional processing and social decision-making, two social cognitive processes involving the perceptions of others intentions, in healthy participants with natural variation in paranoid thinking. We hypothesized that paranoid thinking would predict shameful feelings when the victim of deliberate (but not accidental) harm on the Moral Emotions task. We also hypothesized that distrust-based punishment behavior would be greatest when playing against a suspicious opponent on the Prisoner's Dilemma, and that stealing would be associated with paranoid thinking. Finally, we hypothesized that sensitivity to fairness would not be impaired on the Ultimatum Game.

Emotional Moral Processing

Regression analyses offered some support for hypothesis one, revealing that almost half of the variance in shameful feelings was predicted by delusional ideation when the victim of intentional harm by another person. This effect was maintained even when including measures of depression and cognitive flexibility in the model. Although we expected paranoid thinking to be the key predictor, correlational analyses confirmed that trait paranoia and delusion vulnerability were moderately associated, as expected. In line with our hypothesis, no trait measures were significantly associated with either moral emotion when the victimiser of accidental or deliberate harm. However, trait measures relevant to paranoia and psychosis were positively associated with moral emotions when the victim of a harmful action, thus supporting that paranoia is specific to the experience of harm by others. This is consistent with previous studies showing that victimization (i.e., "he/she punished me, so I must have done something wrong") is a key social risk factor for increased vulnerability to psychosis (20, 50). It is also likely that perceived social rank, particularly if viewing oneself in a lower out-group from the majority, exacerbates

feelings of inferiority in those with pre-existing paranoia (32).

Cognitive models of persecutory delusions implicate altered emotional processes in their persistence (9, 10). For example, negative self-evaluations have been shown to be associated with positive symptoms in patients with schizophrenia (51) as well as with paranoia in the general population (52). Delusional beliefs may be particularly resistant to change if they are held in congruence with negative self-schemas (9). Shameful feelings in response to deliberate harm are more consistent with activation of negative schemas about the self ("Bad Me" paranoia) rather than the protection against distress from others ("Poor Me" paranoia) (53). Shame is strongly associated with the frequency and distress of paranoid thinking in patients with psychotic disorders (54), although less is known about its relationship with the content of delusions. As the PDI contains some items of persecution, suspiciousness, and paranoid ideas, it is possible that multidimensional delusional beliefs, including thoughts of persecution, predict shame in response to interpersonal harm. As no trait measure significantly predicted feelings of guilt, our data further suggest that, although conceptually related, negative moral emotions may have distinct manifestations based on different traits or vulnerability to specific pathology. Whereas guilt denotes a more depressive style of thinking, shame implicates other people and is more likely to precipitate self-referential processing when believing that one is the target of hostile actions. It is worth noting that we did not ask participants to make causal attributions of the amoral behavior depicted in the scenarios. Shameful feelings may activate negative self-evaluations that one deserves to be persecuted, thus leading to more internal attributions for negative outcomes (20, 55). However, it is also possible that attributions for harm by a perpetrator might directly contrast with emotional response, such that individuals with paranoia would externalize negative events to the victimiser or situation, but still respond in a self-devalued manner [i.e., one is both threatened and weak; (52)]. Although these possibilities cannot be addressed by the current study, findings from this task extend emotional processes implicated in cognitive models of delusions to moral emotions, in which shame may have particular relevance to perceived deservedness in those with elevated paranoia.

Social Decision-Making

Both the Prisoner's Dilemma and Ultimatum Game allowed for the systematic manipulation of an opponent's behavior to enable investigation of cooperation and punishment during social economic exchange games (33). We found that uncooperative behavior on the Prisoner's Dilemma was significantly greater both when the participant and opponent contributed more in comparison with when the participant and opponent contributed equally, possibly reflecting protection of one's own contribution or a sense of entitlement for a larger share of the earnings. The percentage of steals between the participant's and opponent's contributions was not significantly different. This may reflect participants "predicting" that the opponent player would steal from them when the opponent contributed more, thus choosing to inflict punishment at the same tendency as when the participant contributed more, despite a loss in earnings for both players (i.e., participants would rather forfeit all gains then let their opponent succeed). In support of hypothesis two, we found more distrust-based punishment behavior when the opponent used a suspicious strategy of gameplay. In addition, more stealing was associated with higher levels of paranoid thinking, but, somewhat unexpectedly, only when playing against a *cooperative* opponent. Others have shown a positive association between paranoia and choice to compete on this task in the general population, suggesting a behavioral marker of non-clinical paranoia (31). Here, distrust-based punishment behavior was greatest when playing against a suspicious opponent, but paranoid thinking was associated with stealing from the player who always chose to split, thus showing expectation of (and an inability to update beliefs about) unfounded malevolent intentions of another person, despite their full cooperation toward mutually advantageous reward.

Results from the Ultimatum Game supported hypothesis three. It was found that, consistent with previous studies in the healthy population (33, 56, 57), participants generally rejected unfair offers, but accepted significantly more unequal offers when the opponent contributed more. Furthermore, sensitivity to fairness was greatest when the participant contributed the most. There has been some evidence that patients with schizophrenia are less averse to unfairness to their own disadvantage (36), although others have suggested that impaired decision-making may be specific to the presence of psychopathology, symptom severity (either negative and/or cognitive impairments in working memory and executive function), or disrupted connectivity in emotion-related areas of the brain including the anterior cingulate cortex, orbitofrontal cortex, and amygdala (38, 39, 58). Future studies comparing healthy individuals with subclinical paranoia and patients with schizophrenia would help elucidate at what level of severity these possibilities compromise sensitivity to fairness. Lastly, it was found that participants who were more likely to steal on the Prisoner's Dilemma were less likely to accept offers on the Ultimatum Game, thus demonstrating an inverse relationship between cooperation and assertiveness. We note that the relationship between cooperative behavior and reasoning biases are relatively under-investigated in paranoia and suggest that introducing monetary incentives distinguishes reasoning (using the information available to draw inferences) from decision-making (selecting the best option at different levels of risk), as shown in the socioeconomic strategies probed here.

Implications and Conclusions

Overall, the key findings from this study are, firstly, that delusional ideation predicts shameful feelings when the victim of deliberate harm by another person; secondly, that distrust-based punishment behavior is greatest in response to a suspicious opponent, but that inflicting punishment on a cooperative opponent relates to increased paranoid thinking; and thirdly, that sensitivity to fairness remains intact when economically disadvantaged. As this study included relatively young adults, future studies should replicate these findings in samples better representative of patients with schizophrenia. Use of virtual reality methods and an actual or confederate opponent (rather than avatar) would also improve the genuineness of social

interactions involving the perception of the intentions of others. Clinical implications include increased specificity of impaired emotional processes in cognitive models of threat beliefs (9, 10), in which shameful feelings in response to deliberate harm were shown to be one type of negative self-evaluation predicted by delusion proneness. Furthermore, expectation of treatment, which differs on the basis of one's perceived social rank (e.g., feelings of inferiority irrespective of other people's intentions, hostile, or not), is likely to precipitate social interactions with negative outcomes. For example, punishing a suspicious opponent may be advantageous, but paranoid thoughts associated with punishing a cooperative opponent will have implications for reduced pro-social behavior. Expectation of unfair treatment is also likely to decrease self-reflection about one's own worth, which in turn decreases ability to understand the intentions of others (59). Interventions that target social-cognitive deficits [Social Cognition and Interaction Training; (60)], pre-existing biased cognitive mechanisms [e.g., Cognitive Bias Modification for paranoia, CBM-pa; (61)] and metacognition [Metacognitive training, MCT; (62)] including difficulties making sense of the mental states of others [Metacognitive Interpersonal Therapy; (63)] are key approaches for improving social and cognitive outcomes in patients with schizophrenia that act directly on affective domains or modify related underlying cognitive-affective biases. Such interventions may also have a useful application for reducing the social-cognitive effects of paranoia and delusional capacity in the general population. Finally, this study further validated EMOTICOM as a useful neuropsychological battery for assessing affective cognition in non-psychiatric samples (22). The effects of paranoia on social cognitive processes including moral emotions and decision-making warrant further investigation using EMOTICOM at more severe levels of persecutory thinking.

AUTHOR CONTRIBUTIONS

GS conceived and designed the study, obtained ethical approval, collected data, analyzed and interpreted data and wrote the manuscript. HJ, NR, SK, and AZ collected data. TR and BS interpreted data and provided feedback on the manuscript.

FUNDING

This project was funded by the Department of Psychology, University of Cambridge. GS was funded by grants from Eton College and The Wallitt Foundation and is supported by the NIHR Cambridge Biomedical Research Centre (BRC) Mental Health Theme. Barbara Sahakian receives funding from the NIHR Cambridge Biomedical Research Centre (BRC) Mental Health Theme. EMOTICOM was funded by a grant from the Medical Research Council (MRC) to Rebecca Elliott, BS, TR, Jonathan Roiser and Mitul Mehta (MR/J011894/1).

REFERENCES

1. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. *Nat Rev Neurosci.* (2015) 16:620–31. doi: 10.1038/nrn4005
2. Birchwood M. Pathways to emotional dysfunction in first-episode psychosis. *Br J Psychiatry* (2003) 182:373–5. doi: 10.1192/bjp.182.5.373
3. Mancuso F, Horan WP, Kern RS, Green MF. Social cognition in psychosis: multidimensional structure, clinical correlates, and relationship with functional outcome. *Schizophr Res.* (2011) 125:143–51. doi: 10.1016/j.schres.2010.11.007
4. Pinkham AE, Harvey PD, Penn DL. Paranoid individuals with schizophrenia show greater social cognitive bias and worse social functioning than non-paranoid individuals. *Schizophr Res Cogn.* (2016) 3:33–8. doi: 10.1016/j.scog.2015.11.002
5. Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L. The relationship between neurcognition and social cognition with functional outcome in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev.* (2011) 35:573–88. doi: 10.1016/j.neubiorev.2010.07.001
6. Frith CD. *The Cognitive Neuropsychology of Schizophrenia.* Lawrence Erlbaum Associates (1992).
7. Freeman D, Garety PA. Comments on the content of persecutory delusions: does the definition need clarification? *Br J Clin Psychol.* (2000) 39:407–14. doi: 10.1348/014466500163400
8. Freeman D. Suspicious minds: the psychology of persecutory delusions. *Clin Psychol Rev.* (2007) 27:425–57. doi: 10.1016/j.cpr.2006.10.004
9. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med.* (2001) 31:189–95. doi: 10.1017/S0033291701003312
10. Freeman D, Garety PA, Kuipers E, Fowler D, Bebbington PE. A cognitive model of persecutory delusions. *Br J Clin Psychol.* (2002) 41:331–47. doi: 10.1348/014466502760387461
11. Huq S, Garety P, Hemsley D. Probabilistic judgments in deluded and non-deluded subjects. *Q J Exp Psychol A* (1988) 40:801–12. doi: 10.1080/14640748808402300
12. Savulich G, Freeman D, Shergill S, Yiend J. Interpretation biases in paranoia. *Behav Ther.* (2015) 46:110–24. doi: 10.1016/j.beth.2014.08.002
13. Savulich G, Shergill S, Yiend J. Interpretation biases in clinical paranoia. *Clin Psychol Sci.* (2017) 5:985–1000. doi: 10.1177/2167702617718180
14. Brüne M. Emotion recognition, 'theory of mind,' and social behaviour in schizophrenia. *Psychiatry Res.* (2005) 133:135–47. doi: 10.1016/j.psychres.2004.10.007
15. Lysaker PH, Salvatore G, Grant MLA, Procacci M, Olsek KL, Buck KD, et al. Deficits in theory of mind and social anxiety as independent paths to paranoid features in schizophrenia. *Schizophr Res.* (2010) 124:81–5. doi: 10.1016/j.schres.2010.06.019
16. Lysaker PH, Yanos PT, Outcalt J, Roe D. Association of stigma, self-esteem and symptoms with concurrent and prospective assement of social anxiety in schizophrenia. *Clin Schizophr Relat Psychoses* (2010) 4:41–8. doi: 10.3371/CSRP.4.1.3
17. Salvatore G, Lysaker PH, Popolo R, Procacci AC, Dimaggio G. Vulnerable self, poor understanding of other's minds, threat anticipation and cognitive biases as triggers for delusional experience in schizophrenia: a theoretical model. *Clin Psychol Psychother.* (2012) 19:247–59. doi: 10.1002/cpp.746
18. Savulich G, Shergill S, Yiend J. Biased cognition in psychosis. *J Exp Psychopathol.* (2012) 3:514–36. doi: 10.5127/jep.016711
19. Kinderman P, Bentall RP. Causal attributions in paranoia and depression: internal, personal, and situational attributions for negative events. *J Abnorm Psychol.* (1997) 106:341–5. doi: 10.1037/0021-843X.106.2.341
20. Bentall RP, Corcoran R, Howard R, Blackwood N, Kinderman P. Persecutory delusions: a review and theoretical integration. *Clin Psychol Rev.* (2001) 8:1143–92. doi: 10.1016/S0272-7358(01)00106-4
21. Garety PA, Freeman D. Cognitive approaches to delusions: a critical review of theories and evidence. *Br J Clin Psychol.* (1999) 38:113–54. doi: 10.1348/014466599162700
22. Bland AR, Roiser JP, Mehta MM, Schei T, Boland H, Campbell-Meiklejohn DK, et al. EMOTICOM: a neuropsychological test battery to evaluate emotion, motivation, impulsivity, and social cognition. *Front Behav Neurosci.* (2016) 10:25. doi: 10.3389/fnbeh.2016.00025

23. O'Connor LE, Berry JW, Weiss J. Interpersonal guilt, shame, and psychological problems. *J Soc Clin Psychol.* (1999) 18:181–203.
24. Tangney JP, Stuewig J, Mashek DJ. Moral emotions and moral behavior. *Ann Rev Psychol.* (2007) 58:345–72. doi: 10.1146/annurev.psych.56.091103.070145
25. Johnson J, Jones C, Lin A, Wood S, Heinze K, Jackson C. Shame amplifies the association between stressful life events and paranoia amongst young adults using mental health services: implications for understanding risk and psychological resilience. *Psychiatry Res.* (2014) 220:217–25. doi: 10.1016/j.psychres.2014.07.022
26. Matos M, Pinto-Gouveia J, Gilbert P. The effect of shame and shame memories on paranoid ideation and social anxiety. *Clin Psychol Psychother.* (2013) 20:334–9. doi: 10.1002/cpp.1766
27. Fehr E, Camerer CF. Social economics: the neural circuitry of social preferences. *Trends Cogn Sci.* (2007) 11:419–27. doi: 10.1016/j.tics.2007.09.002
28. Frith CD, Singer T. The role of social cognition in decision making. *Philos Trans R Soc Lond B Bio Sci.* (2008) 363:3875–86. doi: 10.1098/rstb.2008.0156
29. Poundstone W. *Prisoner's Dilemma.* New York, NY: Doubleday (1992).
30. Güth W, Schmittberger R, Schwarze B. An experimental analysis of ultimatum bargaining. *J Econ Behav Org.* (1982) 3:367–88. doi: 10.1016/0167-2681(82)90011-7
31. Ellett L, Allen-Crooks R, Stevens A, Wildschut T, Chadwick T. A paradigm for the study of paranoia in the general population: the Prisoner's Dilemma Game. *Cogn Emot.* (2013) 27:53–62. doi: 10.1080/02699931.2012.689757
32. Raihani NJ, Bell V. Conflict and cooperation in paranoia: a large-scale behavioural experiment. *Psychol Med.* (2017) 48:1523–31. doi: 10.1017/S0033291717003075
33. Bland AR, Roiser JP, Mehta MM, Schei T, Sahakian BJ, Robbins TW, et al. Cooperative behaviour in the ultimatum game and prisoner's dilemma depends on player's contributions. *Front Psychol.* (2017) 8:1017. doi: 10.3389/fpsyg.2017.01017
34. Bolton GE. A comparative model of bargaining: theory and evidence. *Am Econ Rev.* (1991) 81:1096–136.
35. Fehr E, Schmidt K. A theory of fairness, competition, and cooperation. *Q J Econ.* (1999) 114:817–68. doi: 10.1162/003355399556151
36. Csukly G, Polgar P, Tombor P, Rethelyi J, Keri S. Are patients with schizophrenia rational maximisers? Evidence from an ultimatum game study. *Psychiatry Res.* (2011) 187:11–7. doi: 10.1016/j.psychres.2010.10.005
37. de la Asuncion J, Docx L, Sabbe B, Morrens M, de Bruijn ER. Abnormal emotion processing, but intact fairness and intentionality considerations during social decision-making in schizophrenia. *Front Psychol.* (2015) 6:1058. doi: 10.3389/fpsyg.2015.01058
38. Wischniewski J, Brue M. Moral reasoning in schizophrenia: an explorative study into economic decision making. *Cogn. Neuropsychiatry* (2011) 16:348–63. doi: 10.1080/13546805.2010.539919
39. Agay N, Kron S, Carmel Z, Mendlovic S, Levkovitz Y. Ultimatum bargaining behavior of people affected by schizophrenia. *Psychiatry Res.* (2008) 157:39–46. doi: 10.1016/j.psychres.2006.03.026
40. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, et al. The mini international neuropsychiatric interview (MINI). a short diagnostic structured interview: reliability and validity according to the CIDI. *Eur Psychiatry* (1997) 12:224–31. doi: 10.1016/S0924-9338(97)83296-8
41. Green CEL, Freeman D, Kuipers E, Bebbington P, Fowler D, Dunn G, et al. Measuring ideas of persecution and social reference: the Green et al. Paranoid Thought Scales (GPTS). *Psychol Med.* (2008) 38:101–11. doi: 10.1017/S0033291707001638
42. Nelson HE. *National Adult Reading Test (NART): for the Assessment of Premorbid Intelligence in Patients With Dementia: Test Manual*. Windsor: NFER-Nelson (1982).
43. Fenigstein A, Vanable PA. Paranoia and self-consciousness. *J Pers Soc Psychol.* (1992) 62:129–38. doi: 10.1037/0022-3514.62.1.129
44. Peters E, Joseph SA, Garety PA. Measurement of delusional ideation in the normal population: Introducing the PDI (Peters et al. Delusions Inventory). *Schizophr Bull.* (1999) 25:553–76. doi: 10.1093/oxfordjournals.schbul.a033401
45. Bell V, Halligan PW, Ellis HD. The cardiff anomalous perceptions scale (CAPS): a new validated measure of anomalous perceptual experience. *Schizophr Bull.* (2006) 32:366–77. doi: 10.1093/schbul/sbj014
46. Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs AG. *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press (1983).
47. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II Vol. 1*. San Antonio, TX: Psychological Corporation (1996).
48. Martin M, Rubin R. A new measure of cognitive flexibility. *Psychol Rep.* (1995) 76:623–6. doi: 10.2466/pr0.1995.76.2.623
49. Miller GA, Chapman JR. Misunderstanding analysis of covariance. *J Abnorm Psychol.* (2001) 110:40–8. doi: 10.1037/0021-843X.110.1.40
50. Valmaggia LR, Day FL, Kroll J, Laing J, Byrne M, Fusar-Poli P, et al. Bullying victimisation and paranoid ideation in people at ultra high risk for psychosis. *Schizophr Res.* (2015) 168:66–73. doi: 10.1016/j.schres.2015.08.029
51. Barrowclough C, Tarrier N, Humphreys L, Ward J, Gregg L, Andrews B. Self-esteem in schizophrenia: relationships between self-evaluations, family attitudes, and symptomology. *J Abnorm Psychol.* (2003) 112:92–9. doi: 10.1037/0021-843X.112.1.92
52. Fowler D, Freeman D, Smith B, Kuipers E, Bebbington P, Bashforth H, et al. The brief core schema scales (BCSS): psychometric properties and its associations with paranoia and grandiosity in non-clinical and psychosis samples. *Psychol Med.* (2006) 36:749–59. doi: 10.1017/S0033291706007355
53. Trower P, Chadwick P. Pathways to defense of the self: a theory of two types of paranoia. *Clin Psychol.* (1995) 2:263–78.
54. Castilho P, Pinto AM, Viegas R, Carvalho S, Madeira N, Martins MJ. External shame as a mediator between paranoia and social safeness in psychosis. *Clin Psychol.* (2017). doi: 10.1111/cp.12136
55. Melo SS, Taylor JL, Bentall RP. 'Poor me' versus 'bad me' persecution and instability of persecutory ideation. *Psychol Psychother.* (2006) 79:271–87. doi: 10.1348/147608305X52856
56. Rubinstein A. Perfect equilibrium in a bargaining model. *Econometrica* (1982) 50:97–109. doi: 10.2307/1912531
57. Thaler RH. Anomalies: the ultimatum game. *J Econ Persp.* (1988) 2:195–206.
58. Hinterbuchinger B, Kaltenboeck A, Baumgartner JS, Mossaheb N, Friedrich F. Do patients with different psychiatric disorders show altered social decision-making? A systematic review of ultimatum game experiments in clinical populations. *Cogn Neuropsychiatry* (2018) 23:117–41. doi: 10.1080/13546805.2018.1453791
59. Dimaggio G, Lysaker PH, Carcione A, Nicolò G, Semerari A. Know yourself and you shall know the other…to a certain extent: multiple paths of influence of self-reflection on mindreading. *Conscious Cogn.* (2008) 17:778–89. doi: 10.1016/j.concog.2008.02.005
60. Roberts DL, Penn DL. Social cognition and interaction training (SCIT) for outpatients with schizophrenia: a preliminary study. *Psychiatry Res.* (2009) 166:141–7. doi: 10.1016/j.psychres.2008.02.007
61. Yiend J, Trotta A, Meek C, Dzafic I, Baldus N, Crane B, et al. Cognitive Bias Modification for paranoia (CBM-pa): study protocol for a randomised controlled trial. *Trials* (2017) 18:298. doi: 10.1186/s13063-017-2037-x
62. Moritz S, Woodward TS. Metacognitive training in schizophrenia: from basic research to knowledge translation and intervention. *Curr Opin Psychiatry* (2007) 20:619–25. doi: 10.1097/YCO.0b013e3282f0b8ed
63. Dimaggio G, Montano A, Popolo R, Salvatore G. *Metacognitive Interpersonal Therapy for Personality Disorders*. London: Taylor & Francis (2015).

Conflict of Interest Statement: TR consults for Cambridge Cognition, Lundbeck, Mundipharma, and Unilever and receives royalties for CANTAB from Cambridge Cognition and editorial honoraria from Springer-Verlag and Elsevier. BS consults for Cambridge Cognition, Peak and Mundipharma.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

REVIEW
published: 04 December 2018
doi: 10.3389/fpsyt.2018.00655

Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder

Hannah Zuckerman[1], Zihang Pan[1,2], Caroline Park[1,2], Elisa Brietzke[1,3], Natalie Musial[1], Aisha S. Shariq[1], Michelle Iacobucci[1], Samantha J. Yim[1], Leanna M. W. Lui[1], Carola Rong[1] and Roger S. McIntyre[1,2,4,5,6]**

[1] Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada, [2] Institute of Medical Science, University of Toronto, Toronto, ON, Canada, [3] Department of Psychiatry, Federal University of São Paulo, São Paulo, Brazil, [4] Department of Pharmacology, University of Toronto, Toronto, ON, Canada, [5] Department of Psychiatry, University of Toronto, Toronto, ON, Canada, [6] Brain and Cognition Discovery Foundation, Toronto, ON, Canada

Major Depressive Disorder (MDD) is a prevalent, chronic, disabling, and multidimensional mental disorder. Cognitive dysfunction represents a core diagnostic and symptomatic criterion of MDD, and is a principal determinant of functional non-recovery. Cognitive impairment has been observed to persist despite remission of mood symptoms, suggesting dissociability of mood and cognitive symptoms in MDD. Recurrent impairments in several domains including, but not limited to, executive function, learning and memory, processing speed, and attention and concentration, are associated with poor psychosocial and occupational outcomes. Attempts to restore premorbid functioning in individuals with MDD requires regular screenings and assessment of objective and subjective measures of cognition by clinicians. Easily accessible and cost-effective tools such as the THINC-integrated tool (THINC-it) are suitable for use in a busy clinical environment and appear to be promising for routine usage in clinical settings. However, antidepressant treatments targeting specific cognitive domains in MDD have been insufficiently studied. While select antidepressants, e.g., vortioxetine, have been demonstrated to have direct and independent pro-cognitive effects in adults with MDD, research on additional agents remains nascent. A comprehensive clinical approach to cognitive impairments in MDD is required. The current narrative review aims to delineate the importance and relevance of cognitive dysfunction as a symptomatic target for prevention and treatment in the phenomenology of MDD.

Keywords: cognition, cognitive dysfunction, major depressive disorder, functionality, treatment

OPEN ACCESS

Edited by:
Catherine Harmer,
Warneford Hospital, United Kingdom

Reviewed by:
Mirko Manchia,
Università degli studi di Cagliari, Italy
Larry Culpepper,
Boston University, United States

****Correspondence:***
Hannah Zuckerman
hannahzuckerman2@gmail.com
Roger S. McIntyre
roger.mcintyre@uhn.ca

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *06 June 2018*
Accepted: *16 November 2018*
Published: *04 December 2018*

Citation:
Zuckerman H, Pan Z, Park C, Brietzke E, Musial N, Shariq AS, Iacobucci M, Yim SJ, Lui LMW, Rong C and McIntyre RS (2018) Recognition and Treatment of Cognitive Dysfunction in Major Depressive Disorder. Front. Psychiatry 9:655. doi: 10.3389/fpsyt.2018.00655

INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent, often chronic, and highly disabling multidimensional psychiatric illness affecting ∼350 million individuals worldwide (1). Epidemiological research suggests that depression constitutes the leading cause of disability worldwide (1). MDD is characterized by short- and/or long-term impairment affecting areas including, but not limited to, mood, affect, motivation, and cognition, and is frequently correlated with significant reductions in quality of life and psychosocial functioning (2). Despite therapeutic

advances in MDD, an estimated 70% of patients do not achieve remission following first-line antidepressant medication (3). Moreover, a significant percentage of patients that successfully achieve conventional symptomatic remission (i.e., reduction in total depressive symptom severity) do not return to premorbid functioning (4). The lack of full functional recovery results in decreased workplace functionality and productivity, further contributing to the significant economic burden imposed by MDD, with an accumulated annual loss of $43 billion in North America (5, 6).

Several regions of the brain, including the hippocampus, are negatively implicated in the pathophysiology MDD. Hippocampal size has been demonstrated to be inversely correlated with illness duration, whereby smaller hippocampal sizes have been associated with more severe histories of depression (7). Size has also been shown to be influenced by the number of past hospitalizations and recurrence of the disorder. Frequent, chronic and lengthy states of depression impart impairing effects on brain function, debasing human capital. Without adequate treatment, brain recovery may be compromised, resulting in negative downstream effects on the global functional outcomes in MDD. Amongst the disparate domains affected in depression, cognition is the most relevant dimension related to the loss of human capital. While MDD treatment efforts have focused on clinically observed symptomatic targets including depressed mood and anhedonia, emerging evidence has dissociated symptomatic improvement in these domains from functional improvement and timely return-to-work (8). The foregoing transition highlights the necessity for novel targets more closely associated with the restoration of premorbid psychosocial functioning. Toward this aim, cognitive dysfunction has emerged as a key mediator subserving adverse functional impairment in MDD (9–12).

Cognition is a nons-pecific term that refers to mental processes associated with thinking, learning, and memory (13). Cognitive dysfunction can be defined as a transnosological domain serving as an essential mediator of disparate mental disorders (14). Clinical presentation of MDD, as defined by the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), includes cognitive impairment as a criterion item of a Major Depressive Episode (MDE) (15). Self-reported measures of diminished concentration and attention are frequently observed in individuals presenting with MDE as part of MDD. Moreover, when treating MDD, cognitive impairments are often found to persist during periods of symptomatic remission (14), supporting the disconnect between emotional and functional improvement. While cognitive symptoms may indirectly improve as a consequence of standard antidepressant care, cognitive dysfunction is believed to be a core disturbance in subsets of adults with MDD, independent of mood symptoms (16).

MDD fundamentally alters one's perception and interaction with their surrounding environment, affecting not only the social environment but also information and intellectual processing. Insufficiency surrounding remission outcomes amongst individuals with MDD delineates the importance of novel identification and optimization in recognition and treatment avenues. Successful outcomes rely on a heightened focus encompassing the needs of the patient, the provider, and societal perspectives. Recent developments have thus begun to uncover the relevance of cognition as a clinical priority. Hitherto, disturbances in cognitive function have been undermined in their significance in MDD relative to other psychiatric disorder populations, however, accumulating evidence indicates that a disturbance in cognitive function represents a principal determinant of health outcomes in subsets of MDD patients. Cognitive dysfunction in MDD is common, pervasive across multiple subdomains of cognitive function, and provides a principal determinant of health outcomes with respect to the patient, as well as the societal perspectives. Herein, the current narrative review will provide an up-to-date summary of the literature pertaining to the domain of cognitive function in MDD. The current review aims to provide a framework for the conceptualization of cognition in MDD, with particular focus on the relevance, measurements, and treatment strategies explicating depression as a progressive cognitive disorder.

METHODS

The authors conducted a narrative review of studies investigating cognition as a relevant aspect of Major Depressive Disorder. Studies were identified using PubMed/Medline and Google Scholar from inception to June 2018. *MDD* (and/or variants) was cross-referenced with the following search terms: *cognition, cognitive dysfunction, cognitive deficit, cognitive function, functional outcomes, antidepressants,* and *treatment*. Articles informed by observational studies, clinical trials, and review articles relevant to cognition and cognitive impairment in MDD were included. Additionally, the search was augmented through manual review of related terms and citations from article reference lists.

Domains of Cognition

Cognition and emotion are interconnected processes originating from large interacting networks of neurons within the brain. In recent decades, interdisciplinary fields including neurophysiology, and cognitive psychology have shed light on the neural underpinnings of various cognitive functions and processes; however, the current understanding of these phenomena remains rudimentary. Cognition is multidimensional and lacks a singular consensually agreed upon taxonomy. Several typologies have been proposed for the definition and operationalization of cognitive constructs. Amongst these is the conventional typology distinguishing cognitive aspects into four main domains—namely executive function, attention/concentration, learning/memory, and processing speed (17). The aforementioned domains are interconnected yet distinct phenomena. An additional proposed typology was introduced by the RDoC which, although not limited to cognitive domains, it emphasizes disturbances across multiple cognitive subdomains (18, 19). Moreover, the literature has further proposed a clinically relevant taxonomy with two distinct domains—namely, "cold" cognition and "hot" cognition

(20) (**Table 1**). By definition, "cold" cognition refers to non-emotional information processing; therefore, these cognitive processes occur in the absence of emotional engagement and/or motivation. "Cold" cognitive processes are used in the evaluation of neuropsychological function in depression (20) and generally include the following subdomains of cognition: executive function, learning and memory, attention and concentration, and processing speed. Examples of commonly administered objective neuropsychological tests include the Rey Auditory Verbal Learning Test (RAVLT) (e.g., acquisition and recall), Trail-Making Test A/B (TMT A/B TMT A: processing speed TMT B: processing speed, executive function i.e., set shifting), and Digit Symbol Substitution Test (DSST processing speed, executive function, learning and memory, attention, and concentration) (12). In contrast, "hot" cognition refers to emotionally-laden cognitive processes; these functions are influenced by the individual's emotional state and may include negative attentional bias, emotionally-linked recall, rumination, and anhedonia (20). However, it is important to note that the weighted significance and distinction between "hot" and "cold" cognition in depressed individuals is non-discrete and there are many overlapping features between the two constructs (20, 21).

Neuropsychological testing reveals important inferences into disruptive pathophysiology of neural brain networks with direct consequences on "cold" cognitive functioning. Neural networks including the prefrontal cortex and cingulate gyrus, subcortical regions in the striatum and thalamus, and temporal lobe structures including the amygdala and hippocampus are found to be functionally altered in depressive states (22). More specifically, deficits in executive functioning have been associated with pathophysiology in the lateral aspects of the prefrontal cortex. Additionally, memory impairment has been evidenced to be associated with reductions in hippocampal volume which may be a progressive consequence of MDD (22). The circuitry of these structures has formed the targeted basis of various established treatments for depression, however, currently available treatments are not effective in all cases and requires further understanding into the cognitive deficits and neural markers characterizing MDD.

MDD as a Cognitive Disorder

Cognitive deficits in MDD are consistent, replicable, non-specific, and clinically significant. As cognition comprises an important phenomenological domain of MDD, abnormalities in cognition may be used as a prognostic indicator for identifying at-risk individuals and/or assessing disease onset and progression. Manifestation of cognitive deficits are heterogeneous across individuals with MDD and vary depending on disparate individual- and illness-specific factors. For example, the magnitude of cognitive deficits has been demonstrated to be proportionate to the frequency of depressive episodes and duration of illness (7, 12). In keeping with this, individuals with greater depressive symptom severity are more likely to present with cognitive impairments as compared to those with milder illness severity (12). Moreover, a systematic review evaluating clinical progression in affective disorders, including MDD, suggested that cognitive function is associated with the duration and number of prior episodes (23). Unipolar depression has also been found to be associated with an increased risk of developing dementia, commonly understood as the end stage of progression of cognitive disturbances (23).

It is important to note that available studies often include highly heterogeneous populations. This is an important consideration as there are various co-determinants of cognitive function in MDD that may exact mediational and/or moderational effects alongside illness severity and duration. For example, the presence of co-morbid medical and/or psychiatric conditions may exert direct effects on cognitive function and performance (24, 25). Metabolic co-morbidities, such as obesity, have also been associated with cognitive impairments and are commonly observed in depressed individuals (26). In particular, studies have suggested that obesity is correlated with significant deficits in executive functions such as working memory, planning, and executive control (24). In addition, factors such as age (27), age at onset of depression (28), level of education (29), MDD subtype (30), inflammatory status (31), treatment regimen (32), and childhood adversity (33) have also been demonstrated to influence cognitive performance in patients presenting with MDD (**Figure 1**). Significant impairments in cognitive domains have been reported to precede, occur during, and follow an illness episode; therefore, the temporality and/or causality of the association between cognitive impairment and MDEs remains elusive. Although scarce, studies have evaluated cognitive dysfunction as a risk factor for the development of MDD. In a population study evaluating non-depressed individuals between 20 and 64 years of age found that low episodic memory performance was a reliable predictor of depression 3 years post-diagnosis (34). Moreover, a separate study evaluating longitudinal profiles of depressive symptoms in a birth cohort found that depression is associated with neurodevelopmental impairments which may be mediated by cognition (35). Moreover, cognitive functioning may also be used as a predictor of treatment response. In a recently conducted systematic review of studies evaluating early cognitive change as a predictor of treatment response in individuals with MDD ($n = 7$), early changes in cognitive functioning were demonstrated to have a predictive effect on treatment response. More specifically, the results denoted a trend toward early changes in hot cognitive processes (i.e., changed in facial emotion recognition) as a predictor of response in MDD pharmacotherapy (36).

Clinically, cognition has been classified into four subdomains: (1) learning and memory, (2) attention and concentration, (3) executive function, and (4) processing speed. Patients presenting with MDD commonly experience impairments in

TABLE 1 | Hot and cold cognitive processes.

Hot cognition	Cold cognition
Rumination	Executive function
Emotional processing	Processing speed
Anhedonia (reward processing)	Learning and memory
Attentional bias	Attention and concentration

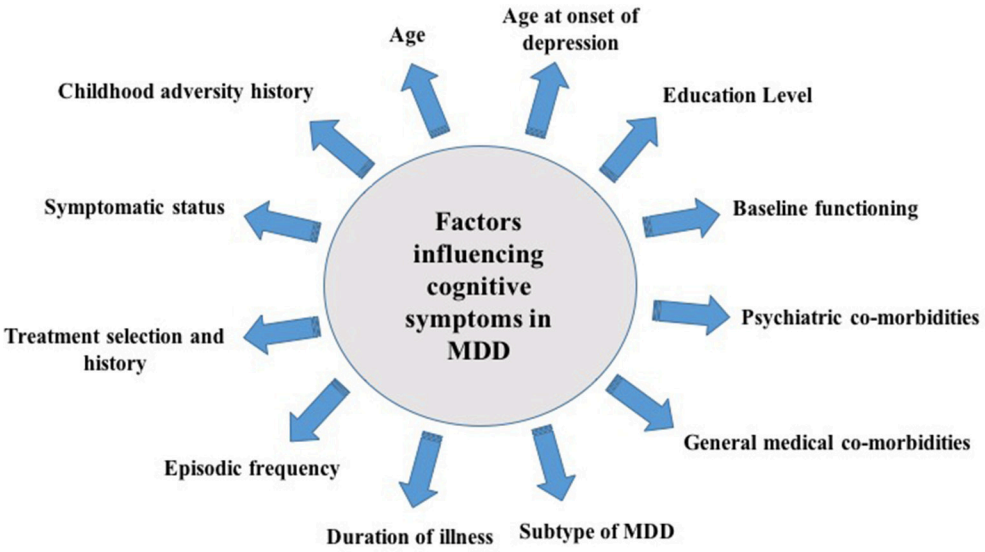

FIGURE 1 | Factors that influence cognitive symptoms in Major Depressive Disorder (MDD).

each of the principal subdomains of cognition, with ∼50% of patients exhibiting deficits of greater than one standard deviation (*SD*) below the mean and 48% of patients two *SD*s below the mean in at least one subdomain (37). Notwithstanding, these reported measures are limited in that they do not necessarily take into consideration subjective cognitive deficits; for example, they may underreport deficits in those individuals whose cognitive performance remains above the mean, but who report deficits in comparison to their baseline level of cognitive function. While MDD does not decrease overall measures of intelligence, cognitive performance across the aforementioned domains have been shown to be severely affected, with effect sizes ranging from 0.2 to 0.8 (14, 38).

Cognitive Impairment in MDD and its Role in Psychosocial Workplace Functioning

Cognitive impairment has been reported to affect function independent of mood symptoms, and has been correlated with functional impairments. The evidence suggests that select symptom domains, such as cognition, may be of greater relevance to overall health outcomes (39). Neurocognitive deficits in this population are directly related to impaired workplace performance, and have significantly contributed to the overall costs associated with depressive illness (12). Individuals with moderate to severe depression have been demonstrated to experience increased rates of unemployment, disability, and absenteeism from work (40). Reductions in workplace productivity and performance has been shown to be mediated by cognitive impairments. For example, one study that evaluated the relationship between depression and role functioning using a population survey found that impairments in attention and concentration mediated the association between depression and impaired role functioning (9). In addition, a *post-hoc* analysis of data from 260 participants enrolled in the International Mood Disorders Collaborative Project (IMDCP) found that in a subpopulation of working adults (18–65 years of age) diagnosed with MDD, cognitive function was a greater determinant of overall workplace performance than total depression symptom severity (41). These observations suggest that cognitive dysfunction is a principal mediator of functional impairment and highlights their relevance in the evaluation and management of outcomes in MDD.

Replicated evidence indicates that disturbances in cognitive function are common both during, and residually following, an acute MDE (12, 42). Moreover, despite depressive symptom remission, individuals have reported continued deficits in cognitive function, which have negative effects on global function, workplace productivity/performance and quality of life (41). For example, a study found that patients who were currently in a state of remission and who met ICD-10 criteria for former MDD experienced persistent cognitive deficits compared to age-, gender-, and education-matched control subjects (42). Although continued research is required to determine which cognitive deficits persist following mood remission, there appears to be documented deficits in the domains of attention and executive performance when compared to healthy controls (42–44).

Measurement and Screening of Cognitive Function

Hitherto, a comprehensive "gold standard" measure of cognitive function in MDD with broad conceptual coverage, sensitivity to change, and immune from practice effects does not yet exist. Limitations of conventional clinical assessment measures [e.g., Hamilton Depression Rating Scale (HAMD), MADRS] are suboptimal insofar as they contain insufficient items assessing cognitive function. Moreover, they are subjective in nature and have been shown to have minimal correlation with

objective measures of cognition (39). Subjective cognition is often influenced by emotional state, and consequently may be affected by the severity of depressive symptoms to a greater extent than objective measures of cognition. Therefore, although subjective measures provide an accurate report of *perceived* cognitive function, it does not necessarily formulate an accurate measure of objective cognitive ability. In clinical practice, a vast array of neurocognitive tests have been employed for the measurement and evaluation of cognitive impairments in MDD [e.g., DSST, TMT, Perceived Deficits Questionnaire (PDQ)]. These conventional instruments are routinely used and frequently administered for the assessment of cognitive function; however, they were not specifically developed or tailored to evaluate MDD-specific cognitive deficits.

Limitations related to the accessibility, cost-effectiveness, and ecological validity of standard tools for measuring cognition in MDD need to be addressed for the improvement of health outcomes in MDD. The THINC-integrated tool (THINC-it) is a recently validated, computerized cognitive assessment battery that screens both objective and subjective cognitive deficits in MDD (45). The THINC-it tool was validated as a sensitive tool in detecting and quantifying the magnitude of cognitive deficits in adults between the ages of 18 and 65 with MDD (45). It effectively evaluates objective measures of cognition through the inclusion of adaptations of four validated tests (i.e., N-Back/Symbol Check, DSST/Codebreaker, TMT-B/Trails, and CRT/Spotter). These tasks accurately assess cognitive subdomains including working memory, visuospatial coordination, set shifting, and psychomotor speed. Additionally, subjective measures of cognition are evaluated through the Perceived Deficits Questionnaire (PDQ-5). Compared to traditional pen-and-paper based cognitive measures such as the DSST, TMT-B and PDQ-5-D, the tool has greater temporal reliability and concurrent validity (45). It is important to note, however, that there are not clear cut-off criteria or precise values for the individual tests that would enhance its use in both diagnosis and treatment response clinically. To our knowledge, the THINC-it is the first freely available computerized tool for screening cognitive dysfunction in MDD. Other developed methods for screening cognitive dysfunction in MDD include the Screen for Cognitive Impairment in Psychiatry (SCIP-D) and the Cognitive Complaints in Bipolar Disorder Assessment (COBRA). The SCIP-D and COBRA have been validated as methods to assess objective and subjective cognitive impairment in MDD, respectively (46). While the COBRA has poorer sensitivity and specificity for the detection of objective dysfunction as compared to the SCIP-D, the SCIP-D has greater sensitivity and specificity for objective dysfunction; therefore, the COBRA can be used in combination with the SCIP-D to increase sensitivity and specificity for the detection of objective dysfunction in MDD (46).

Treatment Interventions Targeting Cognitive Dysfunction in MDD

The evaluation of subsyndromal depressive symptoms (SSD) in patients with MDD is relevant for both treatment selection and outcome. The presence of SSD has been shown to be significantly associated with disability and functional impairments in older adults (47). The pertinence of cognitive dysfunction in MDD underscores the critical importance of developing treatment modalities that are capable of directly and/or indirectly improving cognitive function. Classical pharmacological antidepressant therapy aims to achieve symptomatic remission by targeting mood symptoms; however, residual impairments in cognition that are not sufficiently targeted may impose negative effects on workplace performance and productivity or delay a timely return to work. Targeted treatment of cognitive impairments in MDD may capitalize on modifiable determinants, focusing on prevention and pre-emption.

Cognitive Remediation and Cognitive Therapy

Psychological methods have been proposed for the treatment and management of neurocognitive impairments in disparate neuropsychiatric conditions including MDD (48). Brain imaging evidence in MDD reveals a pattern of increased activity in the limbic system coincident with decreased activity in executive areas of the brain (49). Cognitive remediation (CR) is a psychosocial approach aimed at relieving cognitive impairments in individuals with diverse brain disorders including, but not limited to, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and schizophrenia. Cognitive remediation involves the use of behavioral strategies to exert a beneficial effect across a broad range of functionally-relevant domains (e.g., psychosocial skills). It has been used for the treatment of maladaptive cognitive thought patterns that are prevalent in MDD. Cognitive training has effects on brain structure and function, and has demonstrated effects on neurobiological systems adversely affected in mood disorders such as schizophrenia) (50). Although strong empirical evidence exists for the use of CR in patients with schizophrenia, few studies have been conducted evaluating the efficacy of CR in homogeneous samples of unipolar depressed individuals. When used as an adjunctive therapy in patients with MDD ($n = 12$), CR was found to significantly improve cognitive function (i.e., attention, verbal learning and memory, psychomotor speed, and executive function) compared to patients who were not receiving adjunctive CR (50). The neuropsychological educational approach to remediation (NEAR) has been used as a method of CR that focuses on aspects of motivation and learning. NEAR involves the delivery of individually-tailored and commercially available computer games in a group setting; the games are tailored to an individual's strengths and weaknesses to promote learning via positive reinforcement (51). Significant improvements in cognitive function, particularly verbal memory, have been found in patients with MDD receiving NEAR in addition to routine therapy, as compared to patients receiving only routine therapy R. S. C. (51–53). Although theoretically promising, more evidence is required to suggest that CR is effective for the long-term treatment of cognitive dysfunction in MDD (14). Additional considerations for the improvement and validity of CR for the treatment of cognitive dysfunction in MDD include consistency with regard to task selection (i.e., degree of

difficulty across studies), treatment frequency, and generalizable measurements.

Cognitive behavior therapy (CBT) is a well-studied and propitious therapeutic avenue for the treatment and management of cognitive dysfunction in MDD. The use of CBT in combination with pharmacotherapy in adult depression has been shown to target primarily hot cognitive processes and be more effective than pharmacotherapy alone (54). Notwithstanding, there are a number of patients that do not successfully respond to CBT (55). Consequently, studies have aimed to investigate various subtypes and pathoetiology of depression with the goal of informing possible predictors of treatment response. Several studies have suggested that abnormalities in medial prefrontal cortex (MPFC) (56) and the anterior cingulate cortex (ACC) (57) may contribute to the cognitive impairments observed in MDD. For example, a study found that following CBT treatment, the functional connectivity between MPFC-ACC was significantly reduced. Moreover, symptomatic improvement was positively correlated with a change in MPFC-ACC functional connectivity, (58) suggesting that CBT could potentially be effective as a precognitive intervention.

Neurostimulation

Neurostimulation methods have been shown to be highly effective in the treatment of depression. For example, electroconvulsive therapy (ECT) is a neurostimulation method that has been demonstrated to be efficacious in the acute treatment of depression (59). Negative neurocognitive bias represents a centric feature of major depression that is associated with significant risk of relapse (60), with evidence highlighting negative face processing persisting into periods of remission (61). Previous research provides evidence for various antidepressants as rapid modulators of cognitive and neural emotional face processing, prior to symptom improvement (62, 63). Contrary to this, compounds lacking antidepressant efficacy have no effect on emotional bias (63). The capacity of ECT as a modulator of neurocognitive response to emotional information has recently been studied. In the first conducted double-blind, sham-controlled, parallel-group study, the effect of a single ECT session on the neurocognitive response to emotional information in MDD was evaluated. The results revealed changes in parahippocampal and superior frontal responses to fearful vs. happy faces, as well as in fear-specific functional connectivity between amygdala and occipito-temporal regions in response to single-session ECT treatment (64). Although no statistically significant shift in the neural response to faces was observed following ECT, the trend is suggestive of early shifts in emotional processing that contribute to the antidepressant activity of ECT (64).

Despite its promising use in the reversal of heightened neurocognitive response in MDD, the use of ECT is prejudiced due to reports of cognitive impairments following individual treatment. Some patients report acute disorientation and cognitive deficits, with uncertainty surrounding the duration of the short- and long-term cognitive deficits. In a meta-analysis of 84 studies and 2,981 patients that aimed to evaluate the cognitive impairments following ECT, significant cognitive impairments (i.e., in verbal and visual episodic memory and executive function) were identified in depressed patients within 3 days of treatment. However, these deficits in cognitive function following ECT did not persist beyond 15 days post-treatment, with small to medium effect sizes of improvement for most variables (i.e., processing speed, verbal working memory, and executive function)(59).

More recently, repetitive transcranial magnetic stimulation (rTMS) has emerged as a neurostimulation method for improving neurocognitive function in patients with MDD, and is generally viewed more favorably due to its less invasive nature and diminished propensity for cognitive impairment (65). A systematic review analyzing the role of rTMS in improving neurocognition in patients with treatment-resistant depression (TRD) found that the majority of studies support an association between rTMS and improved neurocognitive effects (66). Much of the literature focuses on the dorsolateral prefrontal cortex (DLPFC) as a target for rTMS as it is a critical brain region for neurocognitive performance (67). Stimulation of the DLPFC through rTMS has been shown to produce variable improvements in psychomotor speed, attention, verbal fluency, executive function, and other working memory domains in patients with TRD (66). The foregoing evidence suggests potential procognitive effects following neurostimulation via rTMS. However, it remains to be determined whether rTMS and/or other neurostimulation techniques can reliably and effectively ameliorate cognitive dysfunction in MDD.

Pharmacotherapy

The counterintuitive gap between remission from depressive symptoms and functional recovery warrants the evaluation of therapeutic avenues targeted at improving cognitive symptoms in individuals with MDD. Notwithstanding the current need for novel targets to facilitate symptomatic remission coincident with functional productivity and timely return-to-work, pharmacotherapies have been scarcely evaluated for their direct and independent effects on cognition in MDD. Individuals with MDD routinely receive interventions [e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), antipsychotics] with potentially adverse effects on cognitive measures (20). Persistent functional impairments mediated by cognitive dysfunction in individuals with MDD warrants the identification of pharmacotherapies with pro-cognitive effects.

Determination of the magnitude of effect of an antidepressant on cognitive function has posed significant limitations as study designs and assessment methodologies are not standardized in implementation. Notwithstanding these inconsistencies amongst studies, certain pharmacotherapies have demonstrated beneficial effects on cognitive measures of individuals with MDD. A systematic review and meta-analysis that aimed to evaluate the overall effect of antidepressants on cognitive function in MDD revealed that SSRIs/SNRIs have more beneficial effects on memory domains compared to tricyclic antidepressants (TCAs), but exhibit equivalent effects on working memory compared to norepinephrine-dopamine reuptake inhibitors (NDRIs) [60].

Within the class of SSRIs, sertraline was found to have more beneficial effects on psychomotor speed compared to fluoxetine[60]. However, the results from this meta-analysis were limited by small sample sizes and large heterogeneity in cognitive testing which prevented pooling of effect sizes for a single domain. Improved standardization of cognitive assessment tools would be beneficial for future trials evaluating cognitive measures in MDD.

Duloxetine is an FDA-approved SNRI antidepressant medication. An imbalance or deficiency in serotonin and/or norepinephrine system function has been associated with cognitive deficits (68), providing the rationale for the use of SNRIs for the treatment of cognitive dysfunction in MDD. A study comparing cognitive function following either duloxetine or escitalopram treatment found that duloxetine resulted in greater improvements in declarative and working memory compared to escitalopram (69). Moreover, a double-blind, placebo-controlled trial involving elderly patients (ages 65 and older) with recurrent MDD found that 8-week treatment with duloxetine resulted in a significant improvement in composite measures of cognition compared to placebo. In this study, the composite cognitive score was mediated largely by improvement in verbal learning and memory (70). Duloxetine has also been assessed as a pro-cognitive antidepressant in young- to middle-aged subpopulations with MDD. For example, in a 12-week open-label trial, duloxetine was found to significantly improve cognitive function, particularly psychomotor speed (71).

Few studies have evaluated the pro-cognitive effects of other antidepressants for the treatment of cognitive dysfunction in MDD, with the exception of vortioxetine. Vortioxetine is an efficacious multimodal antidepressant that acts through a combination of serotonin reuptake inhibition and receptor activity. The efficacy of vortioxetine (10 or 20 mg/day) on cognition was evaluated in placebo-controlled study of adults between the ages of 18 and 65 with recurrent MDD and a current depressive episode (72). In this study, cognition was assessed using the DSST and RAVLT and significant improvements in objective measures of executive function, attention, and processing speed as well as learning and memory were described as a result of these assessments (72). The efficacy of vortioxetine in improving cognition in elderly patients (>65 years of age) with MDD has also been evaluated, and subsequently compared to the efficacy of duloxetine. Similar to the previous study, the RAVLT and DSST were used to evaluate cognitive performance. Significant improvements on the RAVLT were found in patients treated with duloxetine; however, significant improvements on both the RAVLT and DSST were found in patients treated with vortioxetine (73). The foregoing observation of differential effects on cognition could be mediated by the different mechanisms-of-action of the two drugs. Vortioxetine is a multimodal antidepressant hypothesized to exert its effects via its action on the serotonin reuptake transporter inhibition and cell surface serotonergiv receptors (e.g., 5HT3 and 5HT7). In comparison to duloxetine, the activity of vortioxetine as a 5-HT_{1A} receptor stimulator and 5-HT_3 receptor antagonist may enhance cortical glutamatergic neuronal firing contributing to improved cognitive performance in individuals receiving vortioxetine treatment (73). A recent meta-analysis including nine placebo-controlled, randomized trials demonstrated that vortioxetine had the greatest effects on psychomotor speed, executive control, and cognitive control amongst all antidepressants evaluated for cognitive effects in placebo-controlled trials, whereas duloxetine had the greatest effect on delayed recall (74) Currently, vortioxetine is the only pharmacological agent that has been approved for the treatment of MDD through specific targeting of cognitive dysfunction (75).

As of May 2018, the U.S. FDA has announced that vortioxetine has demonstrated direct independent in clinically relevant improvements in cognitive dysfunction in adults 18–65 with MDD. The FDA recognizes significant improvement in cognitive function in vortioxetine-treated individuals as measured by the DSST when compared to placebo. Vortioxetine product insert update to include this information represents that first time any anti-depressant has an explicit mention regarding pro-cognition in MDD. The use of vortioxetine for the treatment of MDD has additionally been accepted by the European Medicines Agency.

Convergent evidence has implicated ketamine as a rapid-acting antidepressant in subpopulations with MDD that do not respond to conventional antidepressant therapies (76). Coincident with its use as an antidepressant in subanesthetic doses, it has been suggested that ketamine may also improve neurocognitive symptoms in TRD. Despite concerns regarding the effect of ketamine on cognition, replicated evidence in healthy controls has shown that ketamine does not impair recall for previously learned information(77, 78), and no impairments in executive function have been associated with ketamine treatment (79, 80). Additionally, in a subpopulation of TRD patients, ketamine was found to significantly reduce explicit suicidal ideation, as compared to the psychoactive placebo-control, midazolam (81). These findings suggest that ketamine treatment may exert beneficial effects on measures of executive functioning in patients with TRD. It is a testable hypothesis that the anti-suicide effects of ketamine are in part mediated by improvements in executive function (e.g., impulsivity) with ketamine treatment (82). However, the use of ketamine warrants further investigation for its application in the treatment of cognitive symptoms in patients with MDD. Early improvements in cognition have also been suggested to predict the efficacy of ketamine for TRD, implicating effects on cognition in the therapeutic mechanism of ketamine. In particular, lower levels of baseline neurocognitive performance in individuals with TRD were correlated with an increased antidepressant response to ketamine, as indicated by a $\geq$50% reduction in MADRS scores (83).

Additional Agents

Erythropoietin (EPO) is a glycoprotein secreted by the kidneys whose main function is to stimulate red blood cell production in the bone marrow (84). In addition to its hematopoietic role, EPO has been found to play a role in the central nervous system and is essential for neurodevelopment, adult neurogenesis and neuroprotection. Hippocampal EPO exerts neuroprotective and neurotrophic effects that have been demonstrated to enhance cognitive performance in various disease models. When systemically administered at therapeutic levels, EPO can cross the

blood-brain barrier and enhance cognitive function in healthy animals (85). Due to its procognitive effects, EPO has been investigated as a treatment for the cognitive deficits observed in TRD. In double-blind placebo-controlled, parallel-group design study, subjects with clinically-defined unipolar TRD scoring ≥17 on the Hamilton Depression Rating Scale-17 (HAMD-17) were randomized to receive either EPO or saline infusions for 8 weeks. In this study, treatment with EPO significantly enhanced verbal recall and recognition compared to saline, which was maintained at follow-up at 14 weeks (86).

Aerobic/resistance exercise is also evidenced as a beneficial adjunctive therapeutic option for cognitive improvement in MDD (87). Replicated evidence implicates adjunctive exercise as an effective method for reducing depressive symptoms (88), with effects observed at levels commonly recommended for general public health (89). Studies have demonstrated that individuals with mild cognitive impairment who engage in regular exercise exhibit greater improvements in memory compared to those who do not engage in regular exercise (89). In addition, studies in healthy participants have demonstrated improvements in psychomotor speed, attention, visual memory, and spatial planning following engagement in exercise. One study found that 30-min exercise augmentation was associated with significant improvements in executive control processing (87). In a meta-analysis evaluating the effects of exercise on cognitive symptoms in MDD, the researchers found no significant procognitive effect of exercise (90); however, they did find that cognitive function was positively influenced by a combination of physical and cognitive activity as well as lower-intensity interventions with higher adherence rates (90). Of note, the findings of this meta-analysis may be limited by the quality of the data and methodological heterogeneity amongst studies. Continued research that stratifies participants by the type of exercise intervention and baseline characteristics (e.g., education level) is required to characterize the cognitive effects of exercise in depressed populations.

Intranasal insulin has also been investigated as a pro-cognitive agent in the treatment of mood and mental disorders. For example, cognitive performance in both Alzheimer's Disease (91) and Bipolar Disorder (92) has been shown to improve following treatment with intranasal insulin. Insulin availability and/or insulin receptor sensitivity has been implicated in MDD (93). Preclinical and clinical studies have demonstrated procognitive effects of intranasal insulin across multiple subdomains of cognition including learning and memory in both healthy and disease affected populations (91, 93). In a randomized, double-blind, placebo-controlled, crossover trial, although no significant improvements in neurocognitive function was observed with intranasal insulin treatment in individuals with MDD (94), the involvement of insulin receptors in cognitive and emotional processing warrants further investigation.

CONCLUSION

Cognitive dysfunction is a core pathological feature of MDD that is often overlooked and under-evaluated in the diagnosis and treatment of the disorder. It serves as a principal mediator of psychosocial and functionality outcomes, with implications in workplace productivity and imminent return-to-work. Evaluation of both subjective and objective measures of cognition is imminent and relevant for improved functional outcomes in MDD.

Classical therapeutic approaches to MDD are insufficient, with poor existing response rates to first-, and even second-line antidepressant administration. While pharmacological treatment avenues have focused primarily on the recovery of mood symptoms, the evidence indicates that remitted patients continue to exhibit clinically-significant cognitive deficits that impact functional capacity. The inherent disconnect between mood remission and functional remission warrants the development of treatments that specifically target functionally-relevant domains (i.e., cognition). Current clinical paradigms have been insufficiently studied for their direct, independent, and clinically-significant effects on cognition. Vortioxetine is currently the only pharmacological agent approved for use in MDD that has been shown to exert direct and independent pro-cognitive effects. Disparate psychotherapeutic and adjunctive agents have been investigated from a precognitive perspective; however additional research is required to establish their independent efficacies. Based on the evidence, the development of therapeutic strategies that directly target cognitive symptoms, in addition to mood symptoms, in MDD is may be required for successful long-term remission and functional recovery in MDD.

AUTHOR CONTRIBUTIONS

HZ: substantial contributions to the conception and design of the manuscript. Drafting of the intellectual content of the work. ZP: substantial contributions to the conception of the manuscript. CP: drafting of the intellectual content of the work. EB: drafting of the intellectual content of the work. NM: critical revision of the work for content. AS: critical revision of the work for content. MI: critical revision of the work, and assistance in the design of figures. SY: critical revision of the work. LL: critical revision of the work. CR: critical revision of the work. RM: substantial contributions to the conception and design of the manuscript, critical revision of the work.

REFERENCES

1. World Health Organization. *Depression and Other Common Mental Disorders Global Health* Estimates. Geneva: World Health Organization (2017).
2. Carvalho AF, Miskowiak KK, Hyphantis TN, Kohler CA, Alves GS, Bortolato B. et al. Cognitive dysfunction in depression - pathophysiology and novel targets. *CNS Neurol Disord. Drug Targets* (2014) 13:1819–35. doi: 10.2174/1871527313666141130203627
3. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for Clinical Practice. *Am J Psychiatry* (2006) 163:28–40. doi: 10.1176/appi.ajp.163.1.28

4. Stotland NL. Recovery from depression. *Psychiatric Clin North Am.* (2012) 35:37–49. doi: 10.1016/j.psc.2011.11.007
5. Jacobs P, Ohinmaa A, Escober-Doran C, Patterson S, Slomp M. PMH31 measuring the economic burden of depression using patient records. *Value Health* (2009) 12:A356. doi: 10.1016/S1098-3015(10)74750-1
6. Lépine J-P, Briley M. The increasing burden of depression. *Neuropsychiatric Dis Treatmen* (2011) 7:3–7. doi: 10.2147/NDT.S19617
7. Gorwood P, Corruble E, Falissard B, and Goodwin GM. Toxic effects of depression on brain function: Impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *Am J Psychiatry* (2008) 165:731–739. https://doi.org/10.1176/appi.ajp.2008.07040574
8. Zimmerman M, McGlinchey JB, Posternak MA, Friedman M, Boerescu D, and Attiullah N. (2006). Discordance between self-reported symptom severity and psychosocial functioning ratings in depressed outpatients: implications for how remission from depression should be defined. *Psychiatry Res.* (2006) 141:185–91. doi: 10.1016/j.psychres.2005.05.016
9. Buist-Bouwman MA, Ormel J, de Graaf R, de Jonge P, van Sonderen E, Alonso J, and ESEMeD/MHEDEA 2000 investigators, the Esem. 2000. Mediators of the association between depression and role functioning. *Acta Psychiatrica Scand.* (2008) 118:451–8. doi: 10.1111/j.1600-0447.2008.01285.x
10. Gonda X, Pompili M, Serafini G, Carvalho AF, Rihmer Z, Dome P. The role of cognitive dysfunction in the symptoms and remission from depression. *Anna Gener Psychiatry* (2015) 14:27. doi: 10.1186/s12991-015-0068-9
11. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res.* (2006) 145:39–48. doi: 10.1016/j.psychres.2005.11.011
12. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety* (2013) 30:515–27. doi: 10.1002/da.22063
13. Stedman TL. *Stedman's Medical Dictionary for the Health Professions and Nursing.* Holland: Wolters Kluwer Health/Lippincott Williams & Wilkins. (2012).
14. McIntyre RS, Xiao HX, Syeda K, Vinberg M, Carvalho AF, Mansur RB, et al. The Prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. *CNS Drugs* (2015) 29:577–89. doi: 10.1007/s40263-015-0263-x
15. Depressive Disorders. *In Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association. (2013). doi: 10.1176/appi.books.9780890425596.dsm04
16. Bora E, Harrison BJ, Yücel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol Med.* (2013) 43:2017–26. doi: 10.1017/S0033291712002085
17. Harrison JE, Lam RW, Baune BT, McIntyre RS. Selection of cognitive tests for trials of therapeutic agents. *Lancet Psychiatry* (2016) 3:499. doi: 10.1016/S2215-0366(16)30067-0
18. Niciu MJ, Mathews DC, Nugent AC, Ionescu DF, Furey ML, Richards EM, et al. Developing biomarkers in mood disorders research through the use of rapid-acting Antidepressants. *Depress Anxiety* (2014) 31:297–307. doi: 10.1002/da.22224
19. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *Am J Psychiatry* (2014) 171:395–7. doi: 10.1176/appi.ajp.2014.14020138
20. Roiser JP, Sahakian BJ. Hot and cold cognition in depression. *CNS Spectrums* (2013) 18:139–49. doi: 10.1017/S1092852913000072
21. Fossati P, Hevenor Simon J Graham SJ, Grady C, Keightley ML, Fergus Craik M, and Mayberg H. In search of the emotional Self: an fMRI study using positive and negative emotional words. *Article Am J Psychiatry* (1938) 160:1938–45
22. Clark L, Chamberlain SR, Sahakian BJ. Neurocognitive Mechanisms in Depression: Implications for Treatment. *Annu Rev Neurosci.* (2009) 32:57–74. doi: 10.1146/annurev.neuro.31.060407.125618
23. Kessing LV, Andersen PK. Evidence for clinical progression of unipolar and bipolar disorders. *Acta Psychiatrica Scand.* (2017) 135:51–64. doi: 10.1111/acps.12667
24. Cserjési R, Luminet O, Poncelet, A.-S, Lénárd L. Altered executive function in obesity. exploration of the role of affective states on cognitive abilities. *Appetite.* (2009) 52:535–9. doi: 10.1016/j.appet.2009.01.003
25. Larochette A-C, Harrison AG, Rosenblum Y, Bowie CR. Additive Neurocognitive Deficits in Adults with attention-deficit/hyperactivity disorder and depressive symptoms. *Arch Clin Neuropsychol.* (2011) 26:385–95. doi: 10.1093/arclin/acr033
26. Mansur RB, Cha DS, Woldeyohannes HO, Soczynska JK, Zugman A, Brietzke E, et al. Diabetes mellitus and disturbances in brain connectivity: abidirectional relationship? *Neuromol Med.* (2014) 16:658–68. doi: 10.1007/s12017-014-8316-8
27. Thomas AJ, Gallagher P, Robinson LJ, Porter RJ, Young AH, Ferrier IN, et al. A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychol Med.* (2009) 39:725. doi: 10.1017/S0033291708004042
28. Herrmann LL, Le Masurier M, Ebmeier KP. White matter hyperintensities in late life depression: a systematic review. *J Neurol Neurosurg Psychiatry* (2007) 79:619–24. doi: 10.1136/jnnp.2007.124651
29. Gildengers AG, Butters MA, Chisholm D, Anderson SJ, Begley A, Holm M, et al. Cognition in older adults with bipolar disorder versus major depressive disorder. *Bipolar Disord.* (2012) 14:198–205. doi: 10.1111/j.1399-5618.2012.00995.x
30. Withall A, Harris LM, Cumming SR. A longitudinal study of cognitive function in melancholic and non-melancholic subtypes of major depressive disorder. *J Affect Disord.* (2010) 123:150–7. doi: 10.1016/j.jad.2009.07.012
31. Pan Z, Grovu RC, Cha DS, Carmona NE, Subramaniapillai M, Shekotikhina M, et al. Pharmacological treatment of cognitive symptoms in major depressive disorder. *CNS Neurol Disord. - Drug Targets* (2017) 16:1–9. doi: 10.2174/1871527316666170919115100
32. Herrera-Guzmán I, Gudayol-Ferré E, Herrera-Guzmán D, Guàrdia-Olmos J, Hinojosa-Calvo E, and Herrera-Abarca JE. Effects of selective serotonin reuptake and dual serotonergic–noradrenergic reuptake treatments on memory and mental processing speed in patients with major depressive disorder. *J Psychiatric Res.* (2009) 43:855–63. doi: 10.1016/j.jpsychires.2008.10.015
33. Lemos-Miller A, Kearney CA. Depression and ethnicity as intermediary variables among dissociation, trauma-related cognitions, and PTSD Symptomatology in Youths. *J Nervous Mental Dis.* (2006) 194:584–90. doi: 10.1097/01.nmd.0000230407.12687.ba
34. Airaksinen E, Wahlin Å, Forsell Y, Larsson M. Low episodic memory performance as a premorbid marker of depression: evidence from a 3-year follow-up. *Acta Psychiatrica Scand.* (2007) 115:458–65. doi: 10.1111/j.1600-0447.2006.00932.x
35. Simons CJP, Jacobs N, Derom C, Thiery E, Jolles J, Van Os J, et al. Cognition as predictor of current and follow-up depressive symptoms in the general population. (2009) 120:45–52. doi: 10.1111/j.1600-0447.2008.01339.x
36. Park C, Pan Z, Brietzke E, Subramaniapillai M, Rosenblat JD, Zuckerman H, et al. Predicting antidepressant response using early changes in cognition: a systematic review. *Behav Brain Res.* (2018) 353:154–60. doi: 10.1016/j.bbr.2018.07.011
37. Gualtieri CT, Morgan DW. The frequency of cognitive impairment in patients with anxiety, depression, and bipolar disorder: an unaccounted source of variance in clinical trials. *J Clin Psychiatry* (2008) 69:1122–30.
38. Papakostas GI. Cognitive symptoms in patients with major depressive disorder and their implications for clinical practice. *J Clin Psychiatry* (2014) 75:8–14. doi: 10.4088/JCP.13r08710
39. McIntyre RS, Lee Y. Cognition in major depressive disorder: a "systemically important functional index" (SIFI). *Curr Opin Psychiatry* (2016) 29:48–55. doi: 10.1097/YCO.0000000000000221
40. Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. *Depress Anxiety* (2010) 27:78–89. doi: 10.1002/da.20580
41. McIntyre RS, Soczynska JZ, Woldeyohannes HO, Alsuwaidan MT, Cha DS, Carvalho AF, et al. The impact of cognitive impairment on perceived workforce performance: results from the international mood disorders collaborative project. *Comprehens Psychiatry* (2015) 56:279–82. doi: 10.1016/j.comppsych.2014.08.051

42. Preiss M, Kucerova H, Lukavsky J, Stepankova H, Sos P, Kawaciukova R. Cognitive deficits in the euthymic phase of unipolar depression. *Psychiatry Res.* (2009) 169:235–9. doi: 10.1016/j.psychres.2008.06.042
43. Hasselbalch BJ, Knorr U, Kessing LV. Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord.* (2011) 134:20–31. doi: 10.1016/J.JAD.2010.11.011
44. Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. *J Affect Disord.* (2005) 89:125–35. doi: 10.1016/j.jad.2005.09.006
45. McIntyre RS, Best M, Bowie C, Carmona N, Cha D, Lee Y, et al. The THINC-integrated tool (THINC-it) screening assessment for cognitive dysfunction: validation in patients with major depressive disorder. *J Clin Psychiatry* (2017) 78:873–81. doi: 10.4088/JCP.14m09658
46. Ott CV, Bjertrup AJ, Jensen JH, Ullum H, Sjælland R, Purdon SE, et al. Screening for cognitive dysfunction in unipolar depression: validation and evaluation of objective and subjective tools. *J Affect Disord.* (2016) 190:607–15. doi: 10.1016/j.jad.2015.10.059
47. Mackin RS, Insel P, Tosun D, Mueller SG, Schuff N, Truran-Sacrey D, et al. The effect of subsyndromal symptoms of depression and white matter lesions on disability for individuals with mild cognitive impairment. *Am J Geriat Psychiatry* (2013) 21:906–14. doi: 10.1016/j.jagp.2013.01.021
48. Bowie CR, Gupta M, Holshausen K, Jokic R, Best M, Milev R. Cognitive remediation for treatment-resistant depression. *J Nervous Mental Dis.* (2013) 201:680–5. doi: 10.1097/NMD.0b013e31829c5030
49. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct.* (2008) 213:93–118. doi: 10.1007/s00429-008-0189-x
50. Porter RJ, Bowie CR, Jordan J, Malhi GS. Cognitive remediation as a treatment for major depression: a rationale, review of evidence and recommendations for future research. *Aust N Zeal J Psychiatry* (2013) 47:1165–75. doi: 10.1177/0004867413502090
51. Naismith SL, Redoblado-Hodge MA, Lewis SJG, Scott EM, Hickie IB. Cognitive training in affective disorders improves memory: a preliminary study using the NEAR approach. *J Affect Disord.* (2010) 121:258–62. doi: 10.1016/J.JAD.2009.06.028
52. Lee RSC, Redoblado-Hodge MA, Naismith SL, Hermens DF, Porter MA, Hickie IB. Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric out-patients. *Psychol Med.* (2013) 43:1161–73. doi: 10.1017/S0033291712002127
53. Naismith SL, Diamond K, Carter PE, Norrie LM, Redoblado-Hodge MA, Lewis SJG, et al. Enhancing memory in late-life depression: the effects of a combined psychoeducation and cognitive training program. *Am J Geriatr Psychiatry* (2011) 19:240–8. doi: 10.1097/JGP.0b013e3181dba587
54. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Can J Psychiatry* (2013) 5858:376–85. doi: 10.1177/070674371305800702
55. DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gener Psychiatry* (2005) 62:409. doi: 10.1001/archpsyc.62.4.409
56. Lemogne C, Delaveau P, Freton M, Guionnet S, Fossati P. Medial prefrontal cortex and the self in major depression. *J Affect Disord.* (2012) 136:e1–1. doi: 10.1016/j.jad.2010.11.034
57. Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Ueda K, Suzuki S, Yamawaki S. Rostral anterior cingulate cortex activity mediates the relationship between the depressive symptoms and the medial prefrontal cortex activity. *J Affect Disord.* (2010) 122:76–85. doi: 10.1016/j.jad.2009.06.017
58. Yoshimura S, Okamoto Y, Matsunaga M, Onoda K, Okada G, Kunisato Y, et al. Cognitive behavioral therapy changes functional connectivity between medial prefrontal and anterior cingulate cortices. *J Affect Disord.* (2017) 208:610–4. doi: 10.1016/J.JAD.2016.10.017
59. Semkovska M, and Mcloughlin DM. Objective cognitive performance associated with electroconvulsive therapy for depression: a systematic review and meta-analysis. (2010) 68:568–77. doi: 10.1016/j.biopsych.2010.06.009
60. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Ann Rev Clin Psychol.* (2005) 1:167–95. doi: 10.1146/annurev.clinpsy.1.102803.143916
61. Miskowiak KW, Carvalho AF. "Hot" cognition in major depressive disorder: a systematic review. *CNS Neurol Disord Drug Targets* (2014) 13:1787–803. doi: 10.2174/1871527313666141130205713
62. Miskowiak K, Papadatou-Pastou M, Cowen PJ, Goodwin GM, Norbury R, Harmer CJ. Single dose antidepressant administration modulates the neural processing of self-referent personality trait words. *NeuroImage* (2007) 37:904–11. doi: 10.1016/j.neuroimage.2007.05.036
63. Nathan PJ, Phan KL, Harmer CJ, Mehta MA, Bullmore ET. Increasing pharmacological knowledge about human neurological and psychiatric disorders through functional neuroimaging and its application in drug discovery. *Curr Opin Pharmacol.* (2014) 14:54–61. doi: 10.1016/j.coph.2013.11.009
64. Miskowiak KW, Kessing LV, Ott CV, Macoveanu J, Harmer CJ, Jørgensen A, et al. Does a single session of electroconvulsive therapy alter the neural response to emotional faces in depression? A randomised sham-controlled functional magnetic resonance imaging study. *J Psychopharmacol.* (2017) 31:1215–24. doi: 10.1177/0269881117699615
65. Rasmussen KG. Some considerations in choosing electroconvulsive therapy versus transcranial magnetic stimulation for depression. *J ECT* (2011) 27:51–4. doi: 10.1097/YCT.0b013e3181da84c6
66. Serafini G, Pompili M, Murri MB, Respino M, Ghio L, Girardi P, et al. The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. a systematic review. *Neuropsychobiology* (2015) 71:125–39. doi: 10.1159/000381351
67. Pascual-Leone A, Rubio B, Pallard,ó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* (1996) 348:233–237.
68. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology of neuropsychiatric disorders. *CNS Spectrums.* (2001) 6:663–70. doi: 10.1017/S1092852900001358
69. Herrera-Guzmán I, Herrera-Abarca JE, Gudayol-Ferré E, Herrera-Guzmán D, Gómez-Carbajal L, Peña-Olvira M, et al. Effects of selective serotonin reuptake and dual serotonergic–noradrenergic reuptake treatments on attention and executive functions in patients with major depressive disorder. *Psychiatry Res.* (2010) 177:323–9. doi: 10.1016/j.psychres.2010.03.006
70. Raskin J, Wiltse CG, Siegal A, Sheikh J, Xu J, Dinkel JJ, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry* (2007) 164:900–9. doi: 10.1176/ajp.2007.164.6.900
71. Greer TL, Sunderajan P, Grannemann BD, Kurian BT, Trivedi MH. Does duloxetine improve cognitive function independently of its antidepressant effect in patients with major depressive disorder and subjective reports of cognitive dysfunction? *Depres Res Treatment* (2014) 2014:627863. doi: 10.1155/2014/627863
72. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol.* (2014) 17:1557–67. doi: 10.1017/S1461145714000546
73. Katona C, Hansen T, Kurre Olsen C, Cornelius Katona C. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol.* (2012) 27:15–23. doi: 10.1097/YIC.0b013e3283542457
74. Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. *Int J Neuropsychopharmacol.* (2015) 19:1–13. doi: 10.1093/ijnp/pyv082
75. Lundbeck. *FDA Updates Trintellix® (vortioxetine) Label to Include Data Showing Improvement in Processing Speed, an Important Aspect of Cognitive Function in acute Major Depressive Disorder (MDD).* (2018). Available online at: https://globenewswire.com/news-release/2018/05/02/1495434/0/en/FDA-updates-Trintellix-vortioxetine-label-to-include-data-showing-improvement-in-processing-speed-an-important-aspect-of-cognitive-function-in-acute-Major-Depressive-Disorder-MDD.html (Accessed May 17, 2018)

76. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. *Human Psychopharmacol.* (2015) 30:152–63. doi: 10.1002/hup.2475
77. Perry EB, Cramer JA, Cho H-S, Petrakis IL, Karper LP, Genovese A, et al. Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology.* (2007) 192:253–60. doi: 10.1007/s00213-007-0706-2
78. Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA. Selective cognitive impairments associated with NMDA receptor blockade in humans. *Neuropsychopharmacology* (2005) 30:633–9. doi: 10.1038/sj.npp.1300642
79. Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, et al. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology* (1999) 145:193–204.
80. Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. *Neuropsychopharmacology.* (2004) 29:208–18. doi: 10.1038/sj.npp.1300342
81. Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, et al. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. *Depress Anxiety* (2014) 31:335–43. doi: 10.1002/da.22253
82. Lee Y, Syeda K, Maruschak NA, Cha DS, Mansur RB, Wium-Andersen IK, et al. A new perspective on the anti-suicide effects with ketamine treatment: a procognitive effect. *J Clin Psychopharmacol.* (2016) 36:50–6. doi: 10.1097/JCP.0000000000000441
83. Rong C, Park C, Rosenblat JD, Subramaniapillai M, Zuckerman H, Fus D, et al. Predictors of response to ketamine in treatment resistant major depressive disorder and bipolar disorder. *Int J Environ Res Public Health* (2018) 15:771. doi: 10.3390/ijerph15040771
84. Bunn HF. Erythropoietin. *Cold Spring Harbor Perspect Med.* (2013) 3:a011619. doi: 10.1101/cshperspect.a011619
85. Miskowiak KW, Vinberg M, Harmer CJ, Ehrenreich H, Kessing LV. Erythropoietin: a candidate treatment for mood symptoms and memory dysfunction in depression. *Psychopharmacology* (2012) 219:687–98. doi: 10.1007/s00213-011-2511-1
86. Miskowiak KW, Vinberg M, Christensen EM, Bukh JD, Harmer CJ, Ehrenreich H, et al. Recombinant human erythropoietin for treating treatment-resistant depression: a double-blind, randomized, placebo-controlled phase 2 trial. *Neuropsychopharmacology* (2014) 39:1399–408. doi: 10.1038/npp.2013.335
87. Kubesch S, Bretschneider V, Freudenmann R, Weidenhammer N, Lehmann M, Spitzer M, et al. Aerobic endurance exercise improves executive functions in depressed patients. *J Clin Psychiatry* (2003) 64:1005–12. doi: 10.4088/JCP.v64n0905
88. Callaghan P, Khalil E, Morres I, Carter T. Pragmatic randomised controlled trial of preferred intensity exercise in women living with depression. *BMC Public Health* (2011) 11:465. doi: 10.1186/1471-2458-11-465
89. Stanton R, Reaburn P. Exercise and the treatment of depression: A review of the exercise program variables. *J Sci Med Sport* (2014) 17:177–82. doi: 10.1016/j.jsams.2013.03.010
90. Sun M, Lanctot K, Herrmann N, Gallagher D. Exercise for cognitive symptoms in depression: a systematic review of interventional studies. *Can J Psychiatry* (2018) 63:115–28. doi: 10.1177/0706743717738493
91. Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, et al. Intranasal insulin improves cognition and modulates -amyloid in early AD. *Neurology.* (2008) 70:440–8. doi: 10.1212/01.WNL.0000265401.62434.36
92. McIntyre RS, Soczynska JK, Woldeyohannes HO, Miranda A, Vaccarino A, MacQueen G, et al. A randomized, double-blind, controlled trial evaluating the effect of intranasal insulin on neurocognitive function in euthymic patients with bipolar disorder. *Bipolar Disord.* (2012) 14:697–706. doi: 10.1111/bdi.12006
93. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Archi Neurol.* (2012) 69:29–38. doi: 10.1001/archneurol.2011.233
94. Cha DS, Best MW, Bowie CR, Gallaugher LA, Woldeyohannes HO, Soczynska JK, et al. A randomized, double-blind, placebo-controlled, crossover trial evaluating the effect of intranasal insulin on cognition and mood in individuals with treatment-resistant major depressive disorder. *J Affect Disord.* (2017) 210:57–65. doi: 10.1016/j.jad.2016.12.006

Conflict of Interest Statement: EB has received honoraria as speaker and advisory board member of Daiichy-Sankyo. RM is a consultant to speak on behalf for, and/or has received research support from Allergan, AstraZeneca, Bayer, Bristol-Myers, Squibb, Janssen-Ortho, Eli Lilly, Lundbeck, Merck, Otsuka, Pfizer, Sunovion, Neurocrine, and Takeda.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 18 December 2018
doi: 10.3389/fpsyt.2018.00697

Abnormal Default Mode Network Homogeneity in Treatment-Naive Patients With First-Episode Depression

*Yujun Gao[1], Menglin Wang[2], RenQiang Yu[3], Yaping Li[1], Ying Yang[4], Xiangxiang Cui[1] and Jinou Zheng[1]**

[1] Department of Neurology, The First Affiliated Hospital, Guangxi Medical University, Nanning, China, [2] Department of Otorhinolaryngology and Head and Neck Surgery, The First Affiliated Hospital, Guangxi Medical University, Nanning, China, [3] Department of Radiology, The First Affiliated Hospital, Chongqing Medical University, Chongqing, China, [4] The First Affiliated Hospital, Guangxi Medical University, Nanning, China

Background and Objective: The default mode network (DMN) may be an important component involved in the broad-scale cognitive problems seen in patients with first-episode treatment-naive depression. Nevertheless, information is scarce regarding the changes in network homogeneity (NH) found in the DMN of these patients. Therefore, in this study, we explored the NH of the DMN in patients with first-episode treatment-naive depression.

Methods: The study included 66 patients and 74 control participants matched by age, gender, educational level and health status who underwent resting-state functional magnetic resonance imaging (rs-fMRI) and the attentional network test (ANT). To assess data, the study utilizes NH and independent component analysis (ICA). Additionally, Spearman's rank correlation analysis is performed among significantly abnormal NH in depression patients and clinical measurements and executive control reaction time (ECRT).

Results: In comparison with the control group, patients with first-episode treatment-naive depression showed lower NH in the bilateral angular gyrus (AG), as well as increased NH in the bilateral precuneus (PCu) and posterior cingulate cortex (PCC). Likewise, patients with first-episode treatment-naive depression had longer ECRT. No significant relation was found between abnormal NH values and the measured clinical variables.

Conclusions: Our results suggest patients with first-episode treatment-naive depression have abnormal NH values in the DMN. This highlights the significance of DMN in the pathophysiology of cognitive problems in depression. Our study also found alterations in executive functions in patients with first-episode treatment-naive depression.

Keywords: depression, default mode network, network homogeneity, attentional network test, rest-fMRI

OPEN ACCESS

Edited by:
Catherine Harmer, Warneford Hospital, United Kingdom

Reviewed by:
Andrea Aguglia, University of Genova, Italy
Cassandra Doris Gould van Praag, University of Oxford, United Kingdom

***Correspondence:**
Jinou Zheng
182196363@qq.com

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *05 June 2018*
Accepted: *30 November 2018*
Published: *18 December 2018*

Citation:
Gao Y, Wang M, Yu R, Li Y, Yang Y, Cui X and Zheng J (2018) Abnormal Default Mode Network Homogeneity in Treatment-Naive Patients With First-Episode Depression. Front. Psychiatry 9:697. doi: 10.3389/fpsyt.2018.00697

INTRODUCTION

Depression is a frequent complex disorder of unclear pathogenesis which is typically characterized by persistent feelings of sadness, loss of interest, reduced energy, a pervasive loss of pleasure, cognitive impairment, and vegetative symptoms (1, 2). Depression is currently known to affect a large number of people globally (http://www.who.int/zh/news-room/fact-sheets/detail/depression), being one of the main causes for disability worldwide and having a substantial socio-economic burden (3). Currently available treatments for depression are far from ideal due to high recurrence rates along with frequent and intolerable side-effects (4).

Increasing evidence has shown depression may be regarded as a disorder of neural networks (5, 6). In particular, the default mode network (DMN) has received growing attention. Previous research has found that the DMN is significantly involved in the neurobiology of depression and has been proposed as a biomarker for treatment response, as DMN activity appears to predict levels of depressive rumination (2, 7–9). The DMN comprises several structures: the medial prefrontal cortex (MPFC), the precuneus (PCu), the anterior/posterior cingulate cortex (A/PCC), and the medial, lateral and inferior parietal cortex (10–13). Recently, the lateral temporal gyrus and the cerebellar crus 1 and 2 have been found to participate in DMN connectivity(13, 14). DMN activity is usually higher at rest and decreases during task-related cognitive processes (15). The DMN has been correlated with monitoring external environments, keeping self-consciousness, producing spontaneous thinking, self-related feelings, memory, the process of cognition, negative ruminations, complex self-referential stimuli, and some special mind-states (16–20).

Previous investigation on depression has demonstrated abnormal resting state connectivity in the DMN; however, findings remain inconsistent on whether connectivity is increased (21–23), decreased (24, 25) or even both (26, 27). Recently, a study reported no correlation between the MPFC and the PCC (28). These discrepancies may be due to several aspects. Furthermore, differences in methodology and limited sample sizes can significantly affect results. Factors such as drugs, treatment methods, illness duration and severity can also contribute to DMN abnormalities. For example, antidepressants can reduce functional connectivity in the DMN (29, 30), while both electroconvulsive therapy and transcranial magnetic stimulation have been observed to change functional connectivity in the DMN (31, 32). Hence, studies on first-episode treatment-naive subjects with depression may have the advantage of lessening confounders.

Network homogeneity (NH) has been widely studied in patients with attention-deficit/hyperactivity disorder, somatization, schizophrenia, and their unaffected siblings (6, 33–40). This method studies a given network without specifying the requirement of localization of network abnormalities. Thus, it assesses the homogeneity of a whole network, an aspect of intrinsic network organization that has long been overlooked. As a voxel-wise measurement approach, NH correlates with all other voxels in a provided interest network. For a given voxel, its average correlation is regarded as an NH value. Homogeneity is defined as the time series comparability for a provided voxel or others in a given network. DMN is associated with cognitive functioning, especially executive function. When the brain is performing tasks, the DMN is negatively activated. Based on studies of DMN abnormalities in patients with depression (40), we hypothesizes that patients with first-episode treatment-naive depression show abnormal DMN homogeneity, which may be related to clinical variables such as illness severity and executive control reaction time (ECRT).

MATERIALS AND APPROACHES

Ethics Statement

All subjects signed the written informed consent before participating in this investigation. The study was approved by the ethics committee of the First Affiliated Hospital, Guangxi Medical University and in accordance with the Declaration of Helsinki.

Subjects

This study included 66 patients with first-episode treatment-naive depression and 74 control participants, all of them recruited from the Department of Neurology, Psychology and Radiology of the First Affiliated Hospital of Guangxi Medical University. Patients were diagnosed following criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), by independent assessments from two psychiatrists. We used the 17-item Hamilton Rating Scale for Depression (HRSD-17) to evaluate depression severity. All patients had total scores $\geq$17 in the HRSD-17 on the day of MRI evaluation. The exclusion criteria were: left-handedness; family history of neurological disorders, severe physical illnesses and substance abuse; pregnancy; findings of abnormal cerebral structures after the initial MRI scanning, and the presence of other psychiatric disorders, such as personality disorders or schizophrenia and related disorders. In total, 74 individuals were included in the control group, matched for age, gender, educational status and overall health, and it is noteworthy that exclusion standards are the same for depression patients.

Behavioral Paradigm

The attentional network test (ANT) was designed by Fan et al. (41), which was presented using Eprime and E-Studio software (Psychological Software Tools, Pittsburgh, PA, USA). The standard procedures for ANT were followed (https://www.sacklerinstitute.org/cornell/assays_and_tools/ant/jin.fan/). In the central testing screen, a "+" sign was placed and regarded as the fixation point. A stimulus signal could be generated above or below the central screen in the form of a target → or a foil *. Four situations involved foils: No foil, one foil in the central part, one foil above the central screen and another one below it, and one foil either above or below the central screen. Arrows could appear in the following ways: A single arrow, five arrows in a direction, and five arrows in different directions. Subjects were required to assure target orientation correctly and quickly. ECRT was calculated by subtracting the consistent arrow direction

reaction time (RT) from the inconsistent arrow direction RT. Longer ECRT represents lower efficiency of the executive control network.

Resting-State Functional Magnetic Resonance Imaging

An Achieva 3TMRI scanner (Philips, Netherlands) was utilized for resting-state functional magnetic resonance imaging (rs-fMRI). Patients were asked to lie down and close their eyes but remain awake. A prototype quadrature birdcage head coil filled with foam was used to minimize head movement. Functional imaging had the following parameters: ratio of repetition time to echo time (TR/TE) (2,000/30 ms), slice thickness (5 mm), pitch (1 mm), field of view (240 × 240 mm) and flip angle (90°). On the structural scan (T1-weighted), the following settings were used: spin-echo sequence, repetition time (TR) = 20 ms, echo time (TE) = 3.5 ms, slice thickness = 1 mm, and field of view (FOV) = 24 × 24 cm.

Data Preprocessing

Imaging data from the rs-fMRI was preconditioned using the data processing assistant for resting-state fMRI (DPARSF) software (42) in Matlab. The first 10 time points were removed, and slice time and head motion were rectified to adjust the time series of images so that the brain is in the same position in every image (43, 44). No participants had more than 2 mm of maximal displacement in the x, y, or z axes and more than 2° of maximal rotation. The structure of each patient was registered to its functional image. The structure of each patient was divided, and a template was created to normalize the structures of the patients after they were defined according to the Montreal Neurological Institute (MNI) standard template, the standardization process of the spatial deformation of the modulation and the structure of the voxel size using 1 × 1 × 1 mm. Finally, the use of the structure of each patient to the function of the conversion matrix was also standardized to the MNI space. During the process of functional image normalization, head motion parameters, white matter signal, and cerebrospinal fluid signal were used as removal covariates (Nuisance regression), and voxel size of 3 × 3 × 3 mm was used as functional covariate. The obtained images were subsequently smoothed with an 8 mm full width at half-maximum Gaussian kernel, band pass filtered (0.01–0.1 Hz), and linearly detrended to lessen the effect of low-frequency drifts and physiologic high frequency noise. Several spurious covariates were removed, including a signal from a region centered in the white matter, 6 head motion parameters obtained by rigid body correction, and a signal from a ventricular ROI. The global signal removal may introduce artifacts into the data and distort resting-state connectivity patterns. Furthermore, the regression of the global signal may significantly distort results when studying clinical populations. Therefore, the global signal was preserved (45, 46).

Default Mode Network Identification

Independent component analysis (ICA) was performed using the Group ICA utility to remove DMN components in templates from the GIFT fMRI toolbox (http://mialab.mrn.org/software/#gica) (46). Three procedures from the GIFT toolbox were utilized for ICA analysis: data reduction, separation of independent components and back rebuilding. On the consideration of every component, the voxel-wise one-sample *t*-test set a statistical map and a threshold. Based on Gaussian random field (GRF) theory, $p < 0.01$ represents a significant statistical modification of multiple comparisons. Voxel significance meets requirements at values of $p < 0.01$, and cluster significance values for $p < 0.01$. The study created masks for the parts included in the DMN. Finally, after combination, the DMN masks were utilized in the NH analysis.

Network Homogeneity Analysis

The results of NH analysis were computed through the application of an in-house script in Matlab (33, 34). The DMN masks showed correlation coefficients between a provided voxel and all others. There is a definition of the correlation coefficient in average as the homogeneity of the provided voxel. Then, the averaged correlation coefficients were converted into z values through z-transformation, promoting normal distribution. The resultant values generated the NH map that finally underwent z-transformation for group comparison.

Statistical Analysis

The study computed demographic information such as age, gender, and education degree, as well as imaging data from the patient and control groups. The two-sample *t*-test was applied for the comparison of continuous variables, while the chi-square test was employed to compare categorical data by using the IBM SPSS Statistics 22.0 software. With the purpose of measuring the discrepancies in the NH regional group, the two-sample *t*-test assisted the individual-level NH map into one group-level voxel wise *t*-test analysis. Later, in the DMN mask, through voxel-wise cross-subject statistics, the two-sample *t*-test was employed to analyze the NH maps. GRF theory is applied into the modification of significance level ($p < 0.01$) for multiple comparisons. (GRF corrected, voxel significance: $P < 0.001$; cluster significance: $P < 0.01$).

Correlation Analysis

NH values are withdrawn from abnormal values in brain regions. After the evaluation of data normality, Pearson correlations can be found among the variables with $p < 0.05$ in statistics using the IBM SPSS Statistics 22.0 software.

RESULTS

Subjects' Demographics and Clinical Features

Demographic information of the study participants is presented in **Table 1**. There were no significant discrepancies among the three groups regarding gender, age, and education years. ECRT was longer in the patient group.

DMN Maps as Ascertained by Group ICA

By employing ICA, DMN masks were removed from the control group. The parts involved in the DMN included the bilateral PCC/PCu, MPFC, ventral anterior cingulate cortex (ACC), lateral

TABLE 1 | Characteristics of the participants.

Demographic data	patients($n = 66$)	NC($n = 74$)	T(orx^2)	*P* value
Gender(male/female)	66(30/36)	74(40/34)	0.16	0.45[a]
Age(years)	28.44 ± 7.6611	28.88 ± 6.67	0.36	0.57[b]
Years of education(years)	36 ± 2.40	12.98 ± 2.49	3.91	0.37[b]
HRSD score	25.88 ± 5.26	–	–	–
ECRT	153.13 ± 71.27	87.09 ± 29.78	7.29	0.00[b]

[a] *The p value for gender distribution was obtained by chi-square test.*
[b] *The p value were obtained by two sample t-tests.*
NC, normal control; HRSD, Hamilton Rating Scale for Depression; ECRT, executive control reaction time.

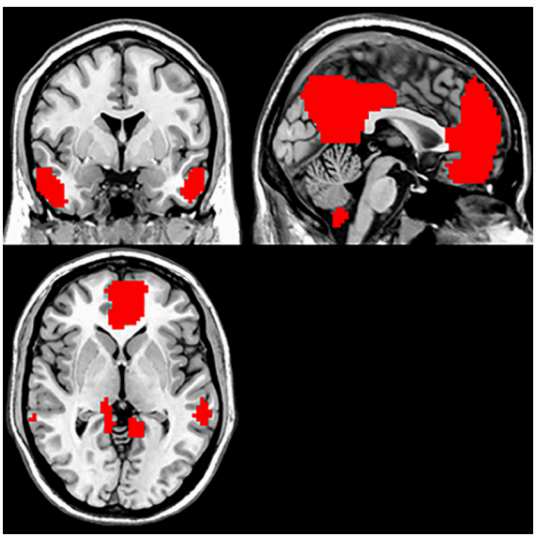

FIGURE 1 | Default mode network (based on group-ICA with threshold at z≥5).

temporal cortex, parietal lobes (medial, lateral, and inferior), and cerebellum Crus 1 and Crus 2 (**Figure 1**).

Group Differences in DMN Regarding NH

The two-sample *t*-test showed significant group discrepancies of NH values between patients and controls within the DMN masks. In comparison with the controls, patients with depression had lower NH in the bilateral AG and significantly higher NH in the bilateral PCC and PCu (**Table 2** and **Figure 2**).

Correlation of NH With Clinical Variables

Significant group discrepancies were found in the six regions where the averaged NH values were withdrawn (bilateral AG, bilateral PCC, and PCu). In the patient group, Pearson linear correlation analysis was implemented to explore the correlations among NH, ECRT, and illness severity. The results showed no significant correlations of NH with those clinical variables.

TABLE 2 | Signification differences in NH values between the groups.

Cluster location	Peak (MNI) X	Y	Z	Number of voxels	*T* value
PATIENTS>CONTROLS					
bilateral PCu	±6	−66	12	609	8.77
Bilateral PCC	±9	−36	27	207	7.45
PATIENTS<CONTROLS					
bilateral AG	±57	−54	27	224	−6.36

MNI, Montreal Neurological Institute; PCu, Precuneus; PCC, posterior cingulate cortex; AG, angular gyrus.

DISCUSSION

In this paper, NH was studied on the DMN of patients with first-episode treatment-naive depression. The latter showed significantly lower NH in the bilateral AG and significantly higher NH in the bilateral PCC and PCu compared to controls. These patients also had longer ECRT. However, no significant correlations were found among NH and illness severity or ECRT in any of the regions.

The cingulate gyrus is an important area where the frontal cortex, insula, amygdala, and hypothalamus interconnect. As a part of the limbic system, it participates in emotion regulation, cognitive function and self-control. PCC represents a core hub for the DMN and plays a key role in integrating self-relative information, retrieval of episodic memory, and autobiographical search. As reported by Maddock (47), unpleasant words can cause significant activation of PCC by task state-fMRI. On the other hand, Hagmann et al. (48) found that PCC can integrate information across the cerebral cortex through a graph theoretic analysis method. According to Marchetti et al. (49), lower fractional anisotropy (FA) values are found in PCC in major depressive disorder. PCC volume is significantly reduced in patients with depression (50, 51). The average metabolic rate of PCC appears to be increased in patients with depression, and can be reduced significantly by antidepressant treatment (52). In addition, a meta-analysis reported the PCC is reliably involved in autobiographical memory, prospection, navigation and theory of mind (53). On the other hand, many studies have observed that functional connectivity decreases in PCC in patients suffering with depression (21–24). One possible interpretation for this paradox is that there is a possible compensatory mechanism. However, some hold that increased PCC is an intrinsic characteristic of depression (54). Our findings suggest the increased NH in the bilateral PCC could contribute to depression.

The PCu—situated in the posterior DMN—intervenes in memory and processing of self-references, while its deactivation has been related to consciousness (55). Abnormal PCu activity can enhance self-references, which favors sleep disorders (56). In this study, we found that increased NH in bilateral PCu demonstrates decreased interaction with the DMN. At least two studies have found that abnormal PCu activity may be related to the genetic risk of depression (57, 58). Therefore, we surmise that

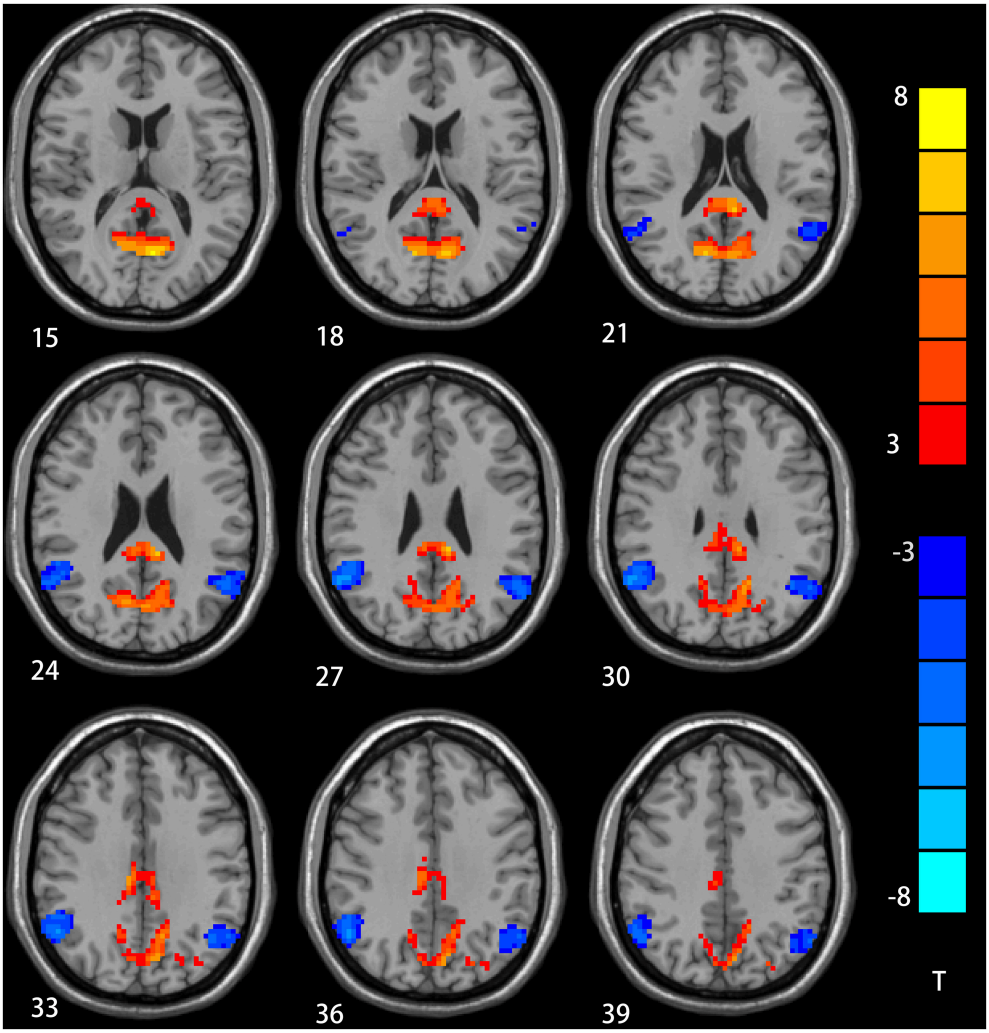

FIGURE 2 | NH differences in the bilateral angular gyrus, enhanced NH in the bilateral precuneus (PCu) and bilateral postal cingulum cortex (PCC) between depression group and control group in statistical maps (Blue denotes lower NH and red denotes higher NH. Meanwhile, color bars point T values obtained from two-sample *t*-test. NH is the abbreviation of network homogeneity).

increased NH values in the bilateral PCu might be associated with depression.

The AG, in the posterior of the inferior parietal lobe, is regarded as a main hub for various subsystems (59). The AG is involved in handling semantics, reading and comprehending words, dealing with numbers, retrieving memory, attention and spatial cognition, social cognition and inference (60). Mulders et al. (32) observed DMN coherence is significantly decreased in the AG in patients with depression. Similarly, Chen et al. found decreased connectivity in the AG within DMN inpatients suffering with first-episode, treatment-naive major depressive disorder, which is associated with higher autobiographical memory scores (61). Patients with depression are thought to have slower thinking and memory loss, which is associated with decreased NH values in bilateral AG.

It is universally acknowledged that the DMN is associated with executive functions, presenting increased activity at rest and decreased activity during the execution of oriented cognitive tasks (62, 63). Therefore, depression patients usually display functional executive impairment and longer ECRT. This parameter is measured by the ANT designed by Fan et al. (41). This test has been applied in the research of other conditions such as Parkinson's disease (64). Longer ECRT represents lower efficiency of the prompt executive control network. Damaged PCC/PCu can affect frontal lobe activity and disrupt execution functions (65). Based on these speculations, abnormal NH, ECRT and illness severity are assumed to be correlated. However, we found no correlations among these factors. This may be because the abnormal NH values in the DMN belong to a characteristic variety for those patients who are not limited by these factors or alternatively are due to the sample size.

Our study had a few limitations. The influence of physiological noises such as cardiac and respiratory rhythm

cannot be completely removed. The sample size was notably restricted. Finally, our study focused only on alterations in the DMN, possibly neglecting significant changes in other brain regions.

Despite these limitations, our study results corroborate the importance of DMN in the pathophysiology of depression by highlighting the presence of abnormal NH values in the DMN of patients with first-episode treatment-naive depression. In addition, we have posited a method for the assessment of NH, which may improve the comprehension of the pathophysiology of depression in future studies.

AUTHOR CONTRIBUTIONS

YG designed experiment and wrote this article. MW, RY, YL, YY, and XC collected and analyzed these data. JZ guided the experiment and revised the article.

ACKNOWLEDGMENTS

The investigation was supported by the grant from the Natural Science Foundation of China (Grant No.81560223). The authors thank all individuals who served as study subjects as well as the reviewers for their proposals and criticisms.

REFERENCES

1. Lebedeva AK, Westman E, Borza T, Beyer MK, Engedal K, Aarsland D, et al. MRI-based classification models in prediction of mild cognitive impairment and dementia in late-life depression. *Front Aging Neurosci.* (2017) 9:13. doi: 10.3389/fnagi.2017.00013
2. Bartova L, Meyer BM, Diers K, Rabl U, Scharinger C, Popovic A, et al. Reduced default mode network suppression during a working memory task in remitted major depression. *J Psychiatr Res.* (2015) 64:9–18. doi: 10.1016/j.jpsychires.2015.02.025
3. Michaud CM, Murray JL, Bloom BR. Burden of disease–implications for future research. *JAMA* (2001) 285:535–9. doi: 10.1001/jama.285.5.535
4. Smith GS, Kramer E, Hermann C, Ma Y, Dhawan V, Chaly T, et al. Serotonin modulation of cerebral glucose metabolism in depressed older adults. *Biol Psychiatry* (2009) 66:259–66. doi: 10.1016/j.biopsych.2009.02.012
5. Hamilton JP, Chen MC, Gotlib IH. Neural systems approaches to understanding major depressive disorder: an intrinsic functional organization perspective. *Neurobiol. Dis.* (2013) 52C:4. doi: 10.1016/j.nbd.2012.01.015
6. Guo W, Liu F, Zhang J, Zhang Z, Yu L, Liu J, et al. Abnormal default-mode network homogeneity in first-episode, drug-naive major depressive disorder. *PLoS ONE* (2014) 9:e91102. doi: 10.1371/journal.pone.0091102
7. Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. Resting-state functional connectivity in major depressive disorder: a review. *Neurosci Biobehav Rev.* (2015) 56:330–44. doi: 10.1016/j.neubiorev.2015.07.014
8. Hamilton JP, Chen G, Thomason ME, Schwartz ME, Gotlib IH. Investigating neural primacy in major depressive disorder: multivariate granger causality analysis of resting-state fMRI time-series data. *Mol Psychiatry* (2011) 16:763–72. doi: 10.1038/mp.2010.46
9. Simon R, Engström M. The default mode network as a biomarker for monitoring the therapeutic effects of meditation. *Front Psychol.* (2015) 6:776. doi: 10.3389/fpsyg.2015.00776
10. Raichle, ME, Snyder AZ. A default mode of brain function. *Proc. Natl. Acad. Sci. U.S.A.* (2001) 98, 676–682. doi: 10.1073/pnas.98.2.676
11. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA.* (2003) 100:253–8. doi: 10.1073/pnas.0135058100
12. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. *Neuroimage* (2007) 37:1083–90. doi: 10.1016/j.neuroimage.2007.02.041
13. Guo W, Liu F, Xue Z, Gao K, Liu Z, Xiao C, et al. Abnormal resting-state cerebellar-cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression. *Progr Neuro Psychopharmacol Biol Psychiatry* (2013) 44:51–7. doi: 10.1016/j.pnpbp.2013.01.010
14. Krienen FM, Buckner RL. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cerebr Cortex* (2009) 19:2485–97. doi: 10.1093/cercor/bhp135
15. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci USA.* (2005) 102:9673–8. doi: 10.1073/pnas.0504136102
16. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron* (2010) 65:550–62. doi: 10.1016/j.neuron.2010.02.005
17. Spreng RN, Grady CL. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *J Cogn Neurosci.* (2010) 22:1112. doi: 10.1162/jocn.2009.21282
18. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proc Natl Acad Sci USA.* (2001) 98:4259. doi: 10.1073/pnas.071043098
19. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. *Science* (2007) 315:393–5. doi: 10.1126/science.1131295
20. Cabeza R, Dolcos F, Graham R, Nyberg L. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage* (2002) 16:317–30. doi: 10.1006/nimg.2002.1063
21. Eyre HA, Yang H, Leaver AM, Van Dyk K, Siddarth P, Cyr NS, et al. Altered resting-state functional connectivity in late-life depression: a cross-sectional study. *J Affect Disord.* (2016) 189:126. doi: 10.1016/j.jad.2015.09.011
22. Cha DS, De Michele F, Soczynska JK, Woldeyohannes HO, Kaidanovich-Beilin O, Carvalho AF, et al. The putative impact of metabolic health on default mode network activity and functional connectivity in neuropsychiatric disorders. *CNS Neurol Disord Drug Targets* (2014) 13:1750–8.
23. Guo W, Liu F, Xue Z, Gao K, Liu Z, Xiao C, et al. Decreased interhemispheric coordination in treatment-resistant depression: a resting-state fMRI study. *PLoS ONE* (2013) 8:e71368. doi: 10.1371/journal.pone.0071368
24. Andreescu C, Tudorascu DL, Butters MA, Tamburo E, Patel M, Price J, et al. Resting state functional connectivity and treatment response in late-life depression. *Psychiatry Res.* (2013) 214:313–21. doi: 10.1016/j.pscychresns.2013.08.007
25. van Tol MJ, Li M, Metzger CD, Hailla N, Horn DI, Li W, et al. Local cortical thinning links to resting-state disconnectivity in major depressive disorder. *Psychol Med.* (2014) 44:2053–65. doi: 10.1017/S0033291713002742
26. Abbott CC, Lemke NT, Gopal S, Thoma RJ, Bustillo J, Calhoun VD, et al. Electroconvulsive Therapy Response in Major Depressive Disorder: A Pilot Functional Network Connectivity Resting State fMRI Investigation. *Frontiers in Psychiatry* (2013) 4:10. doi: 10.3389/fpsyt.2013.00010
27. Wu QZ, Li DM, Kuang WH, Zhang TJ, Lui S, Huang XQ, et al. Abnormal regional spontaneous neural activity in treatment-refractory depression revealed by resting-state fMRI. *Hum Brain Mapp.* (2011) 32:1290–9. doi: 10.1002/hbm.21108
28. Wise T, Marwood L, Perkins AM, Herane-Vives A, Joules R, Lythgoe DJ, et al. Instability of default mode network connectivity in major depression: a two-sample confirmation study. *Transl Psychiatry* (2017) 7:e1105. doi: 10.1038/tp.2017.40
29. Qin J, Wei M, Liu H, Chen J, Yan R, Yao Z, et al. Altered anatomical patterns of depression in relation to antidepressant treatment: Evidence from a pattern

recognition analysis on the topological organization of brain networks. *J Affect Disord* (2015) 180:129–37. doi: 10.1016/j.jad.2015.03.059
30. Gudayolferré E, Perócebollero M, Guàrdiaolmos J. Changes in brain connectivity related to the treatment of depression measured through fMRI: a systematic review. *Front Hum Neurosci.* (2015) 9:582. doi: 10.3389/fnhum.2015.00582
31. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry* (2014) 76:517–26. doi: 10.1016/j.biopsych.2014.01.023
32. Mulders PC, van Eijndhoven PF, Pluijmen J, Schene AH, Tendolkar I, Beckmann CF. Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy. *J Affect Disord.* (2016) 205:130–7. doi: 10.1016/j.jad.2016.06.059
33. Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D, et al. Network homogeneity reveals decreased integrity of default-mode network in ADHD. *J Neurosci Methods* (2008) 169:249–54. doi: 10.1016/j.jneumeth.2007.11.031
34. Guo W, Liu F, Yao D, Jiang J, Su Q, Zhang Z, et al. Decreased default-mode network homogeneity in unaffected siblings of schizophrenia patients at rest. *Psychiatry Res.* (2014) 224:218–24. doi: 10.1016/j.pscychresns.2014.08.014
35. Guo W, Liu F, Chen J, Wu R, Li L, Zhang Z, et al. Olanzapine modulates the default-mode network homogeneity in recurrent drug-free schizophrenia at rest. *Aust N Z J Psychiatry* (2017) 51:1000–9. doi: 10.1177/0004867417714952
36. Guo W, Yao D, Jiang J, Su Q, Zhang Z, Zhang J, et al. Abnormal default-mode network homogeneity in first-episode, drug-naive schizophrenia at rest. *Prog Neuropsychopharmacol Biol Psychiatry* (2014) 49:16–20. doi: 10.1016/j.pnpbp.2013.10.021
37. Wei S, Su Q, Jiang M, Liu F, Yao D, Dai Y, et al. Abnormal default-mode network homogeneity and its correlations with personality in drug-naive somatization disorder at rest. *J Affect Disord.* (2016) 193:81–8. doi: 10.1016/j.jad.2015.12.052
38. Guo W, Liu F, Yu M, Zhang J, Zhang Z, Liu J, et al. Decreased regional activity and network homogeneity of the fronto-limbic network at rest in drug-naive major depressive disorder. *Aust N Z J Psychiatry* (2015) 49:550–6. doi: 10.1177/0004867415577978
39. Zhang D, Wang Y, Lu P, Wang P, Yuan X, Yan J, et al. REST regulates the cell cycle for cardiac development and regeneration. *Nat Commun.* (2017) 8:1979. doi: 10.1038/s41467-017-02210-y
40. Cui X, Guo W, Wang Y, Yang TX, Yang XH, Wang Y, et al. Aberrant default mode network homogeneity in patients with first-episode treatment-naive melancholic depression. *Int J Psychophysiol.* (2017) 112:46–51. doi: 10.1016/j.ijpsycho.2016.12.005
41. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. *J Cogn Neurosci.* (2002) 14:340–7. doi: 10.1162/089892902317361886
42. Chao-Gan Y, Yu-Feng Z. DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Front Syst Neurosci* (2010) 4:13. doi: 10.3389/fnsys.2010.00013
43. Nichols TE, Das S, Eickhoff SB, Evans AC, Glatard T, Hanke M, et al. Best practices in data analysis and sharing in neuroimaging using MRI. *Nat Neurosci.* (2017) 20:299–303. doi: 10.1038/nn.4500
44. Winkler AM, Ridgway GR, Douaud G, Nichols TE, Smith SM. Faster permutation inference in brain imaging. *Neuroimage* (2016) 141:502–16. doi: 10.1016/j.neuroimage.2016.05.068
45. Saad ZS, Gotts SJ, Murphy K, Chen G, Jo HJ, Martin A, et al. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain Connect.* (2012) 2:25–32. doi: 10.1089/brain.2012.0080
46. Hahamy A, Calhoun V, Pearlson G, Harel M, Stern N, Attar F, et al. Save the global: global signal connectivity as a tool for studying clinical populations with functional magnetic resonance imaging. *Brain Connect* (2014) 4:395–403. doi: 10.1089/brain.2014.0244
47. Maddock RJ, Garrett AS, Buonocore MH. Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum Brain Mapp.* (2010) 18:30–41. doi: 10.1002/hbm.10075
48. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, WedeenVJ, et al. Mapping the structural core of human cerebral cortex. *Plos Biol.* (2012) 6:e159. doi: 10.1371/journal.pbio.0060159
49. Marchetti I, Koster EH, Sonuga-Barke EJ, De Raedt R. The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. *Neuropsychol Rev.* (2012) 22:229–51. doi: 10.1007/s11065-012-9199-9
50. Caetano SC, Kaur S, Brambilla P, Nicoletti M, Hatch JP, Sassi RB, et al. Smaller cingulate volumes in unipolar depressed patients. *Biol Psychiatry* (2006) 59:702–6. doi: 10.1016/j.biopsych.2005.10.011
51. Peng J, Liu J, Nie B, Li Y, Shan B, Wang G, et al. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: A voxel-based morphometry study. *Eur J Radiol.* (2011) 80:395. doi: 10.1016/j.ejrad.2010.04.006
52. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol.* (2002) 12:527–44. doi: 10.1016/S0924-977X(02)00102-5
53. Spreng RN, Mar RA, Kim SN. The Common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *MIT Press.* (2009) 21, 489–510. doi: 10.1162/jocn.2008.21029
54. Bonavita S, Sacco R, Esposito S, d'Ambrosio A, Della Corte M, Corbo D, et al. Default mode network changes in multiple sclerosis: a link between depression and cognitive impairment? *Eur J Neurol.* (2017) 24:27–36. doi: 10.1111/ene.13112
55. Maddock RJ, Garrett AS, Buonocore MH. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience* (2001) 104:667–76. doi: 10.1016/S0306-4522(01)00108-7
56. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* (2006) 129:564–83. doi: 10.1093/brain/awl004
57. Gong X, Lu W, Kendrick KM, Pu W, Wang C, Jin L, et al. A Brain-wide association study of DISC1 genetic variants reveals a relationship with the structure and functional connectivity of the precuneus in schizophrenia. *Hum Brain Mapp.* (2014) 35:5414–30. doi: 10.1002/hbm.22560
58. Jang JH, Jung WH, Choi JS, Choi CH, Kang DH, Shin NY, et al. Reduced prefrontal functional connectivity in the default mode network is related to greater psychopathology in subjects with high genetic loading for schizophrenia. *Schizophr Res.* (2011) 127:58. doi: 10.1016/j.schres.2010.12.022
59. Tomasi D, Volkow ND. Association between functional connectivity hubs and brain networks. *Cerebr Cortex* (2011) 21:2003. doi: 10.1093/cercor/bhq268
60. Seghier ML. The angular gyrus: multiple functions and multiple subdivisions. *Neuroscientist* (2013) 19:43–61. doi: 10.1177/1073858412440596
61. Liu P, Yang W, Yuan X, Bi C, Chen A, Huang X. Individual alerting efficiency modulates time perception. *Front Psychol.* (2015) 6:386. doi: 10.3389/fpsyg.2015.00386
62. Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, et al. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci USA.* (2012) 109:2138. doi: 10.1073/pnas.1119598109
63. Sämann PG, Wehrle R, Hoehn D, Spoormaker VI, Peters H, Tully C, et al. Development of the brain's default mode network from wakefulness to slow wave sleep. *Cereb Cortex* (2011) 21:2082–93. doi: 10.1093/cercor/bhq295
64. Boord P, Madhyastha TM, Askren MK, Grabowski TJ. Executive attention networks show altered relationship with default mode network in PD. *Neuroimage Clin.* (2017) 13:1–8. doi: 10.1016/j.nicl.2016.11.004
65. Lautenbacher S, Gauggel, S. *Neuropsychologie Psychischer Störungen.* Berlin Heidelberg: Springer. (2004) 61–62. doi: 10.1007/978-3-662-08959-0

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 01 March 2019
doi: 10.3389/fpsyt.2019.00066

Inflammation, Glutamate, and Cognition in Bipolar Disorder Type II: A Proof of Concept Study

Sinead King[1], Luke A. Jelen[1,2], Charlotte M. Horne[3], Anthony Cleare[1,2], Carmine M. Pariante[1,2], Allan H. Young[1,2] and James M. Stone[1,2,4]*

[1] Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [2] South London and Maudsley NHS Foundation Trust, London, United Kingdom, [3] Department of Psychosis Studies, King's College London, London, United Kingdom, [4] Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

Background: Two current theories regarding the neuroscientific bases of mood disorders involve alterations in glutamatergic neurotransmission and excessive activation of inflammatory pathways. We hypothesized that glutamate (Glu) levels and peripheral inflammatory markers would be associated with cognitive function, in patients with Bipolar Disorder Type II (BP-II), and that such factors would be associated with psychological treatment outcomes.

Aims: The primary aim of this study was to explore the relationship between the neurotransmitter Glu, cytokines (CRP, IL_6, and TNFa) and neuropsychological and related functioning. The secondary aim was to assess cognitive functioning as a predictor of poor response to psychological therapy.

Methods: Proton magnetic resonance spectroscopy data were acquired from the anterior cingulate cortex (ACC) of 15 participants with BP-II, and 13 healthy controls in a 3T magnetic resonance imaging scanner. The Digit Symbol Task (DST) for processing speed, TMT-B for executive function and Rey Auditory Verbal Learning Test (RAVLT) were administered to assess cognitive domains.

Results: There was no significant difference in anterior cingulate Glu, or inflammatory markers between groups. Furthermore, we found no significant difference between groups in any cognitive tests. Scores on the DST were found to be significantly associated with poor response to psychological therapy.

Conclusions: This study may highlight an association between neuropsychological dysfunction and treatment outcome in euthymic patients with BP-II. We did not find any association between peripheral inflammatory markers and brain Glu levels. This may have been in part due to the small sample size.

Keywords: TNFa, cognition, glutamate, bipolar disorder type II, inflammation

OPEN ACCESS

Edited by:
Beata Godlewska, University of Oxford, United Kingdom

Reviewed by:
Mirko Manchia, Università degli Studi di Cagliari, Italy
Luigi Janiri, Catholic University of Sacred Heart, Italy

****Correspondence:***
Sinead King
sinead.king@kcl.ac.uk

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *01 April 2018*
Accepted: *28 January 2019*
Published: *01 March 2019*

Citation:
King S, Jelen LA, Horne CM, Cleare A, Pariante CM, Young AH and Stone JM (2019) Inflammation, Glutamate, and Cognition in Bipolar Disorder Type II: A Proof of Concept Study. Front. Psychiatry 10:66. doi: 10.3389/fpsyt.2019.00066

INTRODUCTION

Mood disorders are highly prevalent and represent a significant public health burden (1). Psychological treatments are thought to be effective modes of treatment for depression and anxiety, yet there are a substantial number of patients who do not benefit (2). It is therefore possible that underlying biological or neuro-psychological mechanisms are involved in preventing patients from fully benefiting from therapy. Due to the severity and co-morbidity of treatment resistant populations, it is likely that patients are not receiving the right treatment to suit their individual needs. To address this problem, more refined approaches are needed to target specific biological and cognitive domains. Two current areas of focus regarding the neuroscientific basis of mood disorders involve alterations in glutamatergic neurotransmission and excessive activation of inflammatory pathways (3).

Since glutamate mediates cognition and behavior (4) and the predominant role of glutamate receptors appears to be the modulation of synaptic plasticity, a property of the brain thought to be vital for memory and learning (5), it is plausible that dysregulation of the glutamatergic system may be involved in treatment resistant mood disorders. Disruption of this system has been consistently implicated in psychiatric illnesses, including major depressive disorder (MDD) and bipolar disorder (BP), in multiple brain areas using proton magnetic resonance spectroscopy (^{1}H-MRS) (3, 6, 7). This technique allows *in vivo* assessment of the chemical composition of tissues in a non-invasive manner, by using the magnetic resonance signal of hydrogen to determine the concentrations of various metabolites, including glutamate.

Studies using single voxel ^{1}H-MRS in the anterior cingulate cortex (ACC), in MDD have consistently reported lower glutamatergic metabolites glutamate (Glu), glutamine (Gln), or Glx (Glu+Gln) (8–12). Studies in bipolar disorder have demonstrated inconsistent results but suggest that levels may be elevated (9, 10, 13). Such inconsistencies may be due to the difference in mood phase between various studies. For example, patients with mania show elevated Glx levels in the left dorsolateral prefrontal cortex (DLPFC) compared with healthy subjects (14). Considering the role of glutamate between subtypes of bipolar disorder (i.e., type I vs. II), Atagun et al. found neurochemical differences in superior temporal cortices (15), i.e., BP-I had significantly lower Glu and glutamate+glutamine (Glx) levels in comparison to BP-II. However, this finding may be due to bipolar disorder type I consistently shown to be taking more anti-psychotic medication (16). Therefore, glutamate concentrations may provide information about neuronal function during a particular mood episode, but also reveal underpinnings that are common/distinct across types.

Indeed, the contribution to altered glutamate release/reuptake activation may be related to cytokine effects within the brain, leading to excitotoxicity and loss of glial elements, consistent with altered effects on cognition and behavior. Preliminary evidence shows that elevated inflammatory markers are associated with elevated glutamatergic neurotransmission (3), which subsequently correlated with poor processing speed. In work investigating how inflammatory markers may impact on the glutamatergic system, it has been shown that patients exposed to the inflammatory cytokine interferon (IFN)-alpha exhibited increased glutamate in left basal ganglia and dorsal anterior cingulate cortex (dACC) in a group of patients with hepatitis C and comorbid depression (17). In turn, high Glx, and Glx/creatine levels have been also been shown to correlate with cognitive impairment in various patient groups (18). A similar process may occur in bipolar disorder, since recent evidence shows elevated glutamate (10) and increased inflammatory markers have also been reported in this patient group (19), albeit in different patients. Increasing evidence is showing increased CRP, IL_6, and TNFa levels in euthymic bipolar patients in comparison to controls (20–22). Furthermore, elevated serum levels of IL-1RA in BP subjects, even during euthymic states, was found to be associated with worse cognitive function (23). Thus, there are some intriguing suggestions that there may be an interaction between inflammation, cognitive impairments and increased brain glutamate levels in BP that require further investigation (24).

The purpose of this study was three-fold. Firstly, we aimed to measure ACC glutamatergic concentrations at rest (i.e., static ^{1}H-MRS) in bipolar disorder type II (BP-II) compared with healthy controls. Second, we aimed to examine any correlations with neuropsychological performance on cognitive tests, and peripheral inflammatory markers (CRP, IL_6, and TNF-a) to investigate cytokine involvement on the glutamatergic system and related effects on cognition and behavior. Lastly, we aimed to assess if the presence of neuropsychological impairment may in turn have subsequent effects on psychological treatment outcomes. We hypothesized that higher levels in Glu, would be associated with poorer cognitive performance in the BP-II group compared with healthy controls and this would be related to the inflammatory cytokines TNFa, CRP, and/or IL_6.

METHODS

Study Subjects

Fifteen patients with BP-II and thirteen healthy controls aged 22–57 years were recruited into the study. The BP-II group were recruited from the Predictors of Outcome Following Psychological Therapy (PROMPT) study which aims to investigate predictors of response to psychological therapy (2). The PROMPT project is a large observational, naturalistic study which investigates predictors of outcome following a range of different psychological therapies, including cognitive behavioral therapy (CBT), guided self-help and counseling, at Southwark Talking Therapies, South London [for more information about the PROMPT study, see (2)]. Healthy controls were recruited through online advertisements. Bipolar patients were assessed for euthymia prior to testing, using short behavioral assessments to assess hypomania and depressive symptoms. However, three people were depressed at the time of their assessment. Exclusion criteria included any serious medical illness, or infection, and substance abuse/dependence within the past 6 weeks (determined by structured clinical interview for DSM-IV). No patients had taken any medications known to affect the immune system

within the past 6 months. 5/15 participants were taking anti-depressant medications including citalopram and fluoxetine due to the difficulty in recruiting patients who were medication free. 10/15 patients were medication free. All participants signed informed consent and the study was approved a priori by the London—Harrow Research Ethics Committee, Ref 12/SC/0528.

Study Procedures

Study procedures occurred in the same order over either 1 or 2 days. ^{1}H-MRS scans were conducted on Day 2, if applicable, between 8 a.m. and 4 p.m. Blood sampling, behavioral assessments and neurocognitive testing were conducted on the same day as the brain scan, and neuropsychiatric assessments were carried out on Day 1 if the session was split into two. Psychological treatments for the BP-II group were delivered by a qualified psychologist or psychological well-being practitioner and all BP-II participants in this present study completed an average of six therapy sessions. Therapy outcome data was extracted from online patient records, as and when patients completed therapy. Depressive symptom severity, using the PHQ-9, is measured after each therapy session and at baseline. Outcome for the present study is defined as the final PHQ-9 score of the last therapy session received by each patient.

Behavioral Assessments

Depression severity was measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) (25). Hypomanic symptoms were assessed using the Young Mania Rating Scale (YMRS) (26). Therapy outcome scores for the 15 BP-II patients, in the form of the Patient Health Qusetionnaire-9 (PHQ-9), were obtained from the outcome phase of the PROMPT study in order to assess baseline predictors of therapy outcome in the present subsample of patients.

Neurocognitive Assessment

Executive function was assessed using the Trail Making Test B and Intra Dimensional Extra Dimensional Shift of the Cambridge Neuropsychological Test Automated Battery. The Rey Auditory Verbal Learning Test (RAVLT) was used to measure verbal learning and memory, and the Digit Symbol Substitution Test of Wechsler Adult Intelligence Scale was used to assess psychomotor processing speed. The Weschler Test of Adult Reading was used to measure pre-morbid IQ.

Scanning Protocol

Scanning was performed on a GE 3-Tesla System (GE, 12-channel head coil). For image guidance and prescription of voxels of interest, axial T1 images were obtained using three-dimensional magnetization-prepared rapid gradient-echo with settings of time to repetition (TR) = 2,000 (ms), time to echo (TE) = 30 ms, time following inversion pulse (TI) = 1,100 ms, flip angle = 8° and voxel size 1 × 1 × 1 mm^3. ^{1}H-MRS was acquired using the standard PRESS sequence with the following parameters: TR = 2,000 ms, TE = 30 ms. See **Figure 1** for our voxel of interest.

^{1}H-MRS Analysis

^{1}H-MRS analysis was accomplished using LCModel. The water-suppressed time-domain data were analyzed between 0.2 and 4.0 ppm. using the basis set provided by the vendor. T1-weighted images were segmented into gray matter, white matter and cerebrospinal fluid (CSF) compartments using Structural Brain Mapping (SPM) software on the whole brain T1 images. A volume of interest was generated on the T1 images, which matched the location and size of ^{1}H-MRS voxel. Volumes of gray matter, white matter and CSF segments in this volume of interest were then calculated. Since the Glu metabolite measures were derived with water-scaling, a further correction was applied to correct the estimated water concentration of the voxel for partial volume CSF contamination. We used the same default CSF, gray matter and white matter water concentrations employed by LCModel (55,556, 43,300, and 35,880 mol/m^3 respectively). For practical purposes, these correction factors were combined into a single equation $M_{corr} = M^*(43{,}300^*gm + 35{,}880^*wm + 55{,}556^*CSF)/[35{,}880^*(1 - CSF)]$, which simplifies to $M^*(1.207^*gm + wm + 1.548\ CSF)/(1 - CSF)$ where M= uncorrected metabolite, wm, white matter fraction; gm, gray matter fraction; and CSF, cerebrospinal fluid faction from the spectroscopy voxel.

Immune Assessments

Blood was obtained in two EDTA tubes and were then immediately stored at −80 °C until batched assay. Concentrations of tumor necrosis factor (TNFa), interleukin 6 (IL_6), and C-reactive Protein (CRP) were assessed in duplicate using multiplex bead-based assays. Blood samples were originally collected from all individuals, however, at analysis stage, some samples could not be found on the sample management system, therefore we were left with 13 BP-II and 10 HC.

Statistical Analysis

Pearson product-moment correlation coefficient was performed to assess the relationship between absolute Glu concentrations in the dorsal Anterior Cingulate Cortex (dACC) and cognitive tests (executive function, verbal learning and psychomotor speed). Secondary analyses examined the relationship between inflammatory markers and absolute Glu concentrations in the dACC. Independent samples T-tests were used to examine the differences in Glu, cognitive tests, and cytokines i.e., TNF-a, IL_6, and CRP levels between groups, as well as age, sex, hypomanic symptoms measured by YMRS and depression severity as measured by the MADRS. All results were assessed for multiple comparisons, using False Discovery Rate (FDR) analysis, in SPSS.

RESULTS

BP-II participants had significantly higher scores on YMRS and MADRS compared to controls (see **Table 1**). There was no significant difference between groups on WTAR. There was a trend for a significant difference between healthy controls and BP-II on the DST and no other significant differences between groups on other cognitive tests, however BP-II tended to perform

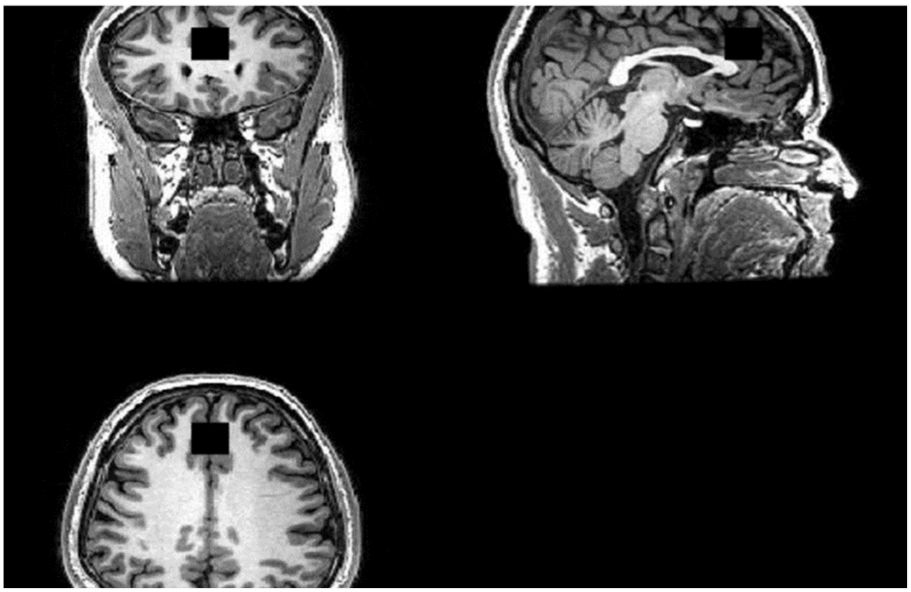

FIGURE 1 | Region of Interest (ROI). ACC Voxel measures 20 (AP) × 20 (RL) × 20 (SI) mm^3 in size and the voxel was prescribed from the midline sagittal localizer, with the center of the voxel placed 16 mm above the genu of corpus callosum perpendicular to the AC–PC line.

TABLE 1 | Mean and standard deviations of clinical and cognitive characteristics.

	Healthy control *n = 13*		Bipolar disorder *n= 15*			
	M	***SD***	***M***	***SD***	***t-value***	***p-value***
YMRS	0.69	1.03	4.36	3.89	3.395	0.004
MADRS	0	0	9.43	12.42	−2.840	0.014
DST	90	18.3	73	24.5	2.005	0.052
RAVLT	56	9.7	51	39.6	1.706	0.996
TMT-B	60.78	36.9	60.85	28.1	−0.005	0.107
WTAR	45.67	4.812	46.21	3.017	−0.341	0.152

TABLE 2 | Co-morbidities in the patient sample (BP-II).

Diagnosis	*N*	%
Suicide risk	8	50%
Panic disorder	6	43%
Agoraphobia	5	31%
OCD	1	6%
PTSD	3	12%
Alcohol dependence	1	6%
Alcohol abuse	1	6%
Psychosis	3	12%
Generalized Anxiety Disorder (GAD)	4	19%

less well. See **Table 1**. The BP-II group had significant psychiatric co- morbidity compared to healthy controls, see **Table 2**.

Bipolar Disorder Type II (BP-II) vs. Healthy Control

Glutamate (Corrected for CSF/Gray/White Matter)

There was no significant difference in anterior cingulate Glu levels between BP-II ($M = 15.92$, $SD = 1.67$) and HC ($M = 15.17$, $SD = 1.50$), $t(-1.420, p = 0.227)$.

Inflammatory Markers

There were no significant differences in TNFa, IL_6, or CRP levels between BP-II and healthy controls. See **Table 3**.

TNFa, IL_6, CRP vs. Glu in BP-II

There were no significant relationships between TNFa ($r = 0.103$, $p = 0.512$), IL_6 ($r = 0.211$, $p = 0.345$), and CRP ($r = 0.356$, $p = 0.435$) with Glu levels in the BP-II group.

Glu vs. Cognitive Data in BP-II

There were no significant relationships between scores on the DST and Glu levels in patients ($r = -0.436$, $p = 0.120$) and no relationship between scores on TMT-B and Glu levels in the BP-II group ($r = 0.194$, $p = 0.524$). There were no significant correlations between Glu and RAVLT or WTAR.

Digit Symbol Task vs. Outcome

Scores on the DST were significantly associated with therapy treatment outcome following psychological therapy ($r = -0.582$, $p = 0.037$), i.e., worse performance on the DST is associated with higher depressive severity following treatment.

DISCUSSION

We found higher levels of CRP, IL_6 and TNFa and elevated levels of dACC Glu in bipolar patients in comparison to controls,

TABLE 3 | BP-II vs. healthy control—TNFa, IL_6, CRP.

	N	*Mean*	*SD*	*p-value*	*t-value*
TNFa					
Healthy control	10	1.7730	0.44242	0.221	−1.322
Bipolar disorder	13	2.0215	0.45284		
IL_6					
Healthy control	10	0.53	0.371	0.792	−0.267
Bipolar disorder	13	0.58	0.479		
CRP					
Healthy control	10	3.02	2.79	0.400	−0.871
Bipolar disorder	13	5.23	4.81		

however the differences were not significant. We found that BP-II subjects tended to perform worse in cognitive tests however the difference were not significant between groups. There was a trend for significance on the DST measure of processing speed ($p = 0.052$) between groups. In turn, we found that reduced processing speed was associated with a poor outcome to psychological treatment.

Our findings contribute to our understanding of neural correlates of Bipolar Disorders that are characterized as having impaired cognitive function (i.e., difficulties in attention and concentration are together, a hallmark of both major depression and hypomania).

LIMITATIONS

The study was designed as a pilot, and as such has a small sample size. As a result, it is possible that some of the negative findings may have been due to a lack of power. Although all patients were assessed as euthymic at screening, three patients were depressed at the time of their scan. Strict euthymic samples should be investigated in further samples. The authors note that although no significant differences were found between groups, the lead author of this study extracted participants who were depressed on the day of the scan and the mean differences in Glu levels between patients and controls were larger, although again, not significantly so. The patients in this study were not excluded based on the use of anti-depressants, given the challenge of recruiting patients with BP-II without medication (12). Although 10/15 patients were not taking anti-depressants, the results could have been influenced by those who were on medication.

CONCLUSIONS

Two evolving theories regarding the development of mood disorders involve excessive activation of inflammatory pathways and alterations in glutamate metabolism. In the present study, we did not find a significant comparison for the involvement of inflammation or in glutamate levels between groups. The reason for this may be in part due to the small sample size, especially as our findings show elevated levels of both cytokines and Glu, which fits with our hypothesis, although not significant. It could also mean that peripheral inflammation is not related to brain Glu in the dACC. Nevertheless, cognitive impairment, and particularly in the area of processing speed, appears to be an important and novel treatment target for improving neuropsychological function in BP-II groups. Improving such factors may lead to better outcomes to psychological therapy and related treatments.

Future work in our group will aim to further characterize the relationship between inflammation, mood and glutamatergic neurotransmission.

AUTHOR CONTRIBUTIONS

SK carried out data collection, all data analyses, and writing of the paper. LJ helped with data collection and preparation. CP provided support and expertise with inflammatory data. AC provided expert guidance and supervision on data analyses and write up. AY provided expert guidance and supervision on write up. JS provided expert guidance and supervision on data analyses and write up. CH helped with data collection and preparation.

FUNDING

This paper represents independent research part funded by the NIHR-Wellcome Trust King's Clinical Research Facility and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

REFERENCES

1. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V., et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol.* (2014) 43:476–93. doi: 10.1093/ije/dyu038
2. Grant N, Hotopf M, Breen G, Cleare A, Grey N, Hepgul N., et al. Predicting outcome following psychological therapy in IAPT (PROMPT): a naturalistic project protocol. *BMC Psychiatry.* (2014) 14:170. doi: 10.1186/1471-244X-14-170
3. Haroon E, Fleischer CC, Felger JC, Chen X, Woolwine BJ, Patel T., et al. Conceptual convergence: increased inflammation is associated with increased basal ganglia glutamate in patients with major depression. *Mol Psychiatry.* (2016) 21:1351–7. doi: 10.1038/mp.2015.206
4. Sanacora G, Treccani G, Popoli M. Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology.* (2012) 62:63–77. doi: 10.1016/j.neuropharm.2011.07.036
5. Morris RG, Frey U. Hippocampal synaptic plasticity: role in spatial learning or the automatic recording of attended experience? *Philos Trans R Soc Lond Ser B Biol Sci.* (1997) 352:1489–503.
6. Taylor R, Neufeld RW, Schaefer B, Densmore M, Rajakumar N, Osuch EA., et al. Functional magnetic resonance spectroscopy of glutamate in schizophrenia and major depressive disorder: anterior cingulate

activity during a color-word Stroop task. *NPJ Schizophr.* (2015) 1:15028. doi: 10.1038/npjschz.2015.28
7. Wise T, Taylor MJ, Herane-Vives A, Gammazza AM, Cappello F, Lythgoe DJ., et al. Glutamatergic hypofunction in medication-free major depression. *J Affect Dis.* (2018) 234:214–9. doi: 10.1016/j.jad.2018.02.059
8. Luykx JJ, Laban KG, van den Heuvel MP, Boks MP, Mandl RC, Kahn RS., et al. Region and state specific glutamate downregulation in major depressive disorder: a meta-analysis of (1)H-MRS findings. *Neurosci Biobehav Rev.* (2012) 36:198–205. doi: 10.1016/j.neubiorev.2011.05.014
9. Gigante AD, Bond DJ, Lafer B, Lam RW, Young LT, Yatham LN. Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. *Bipolar Dis.* (2012) 14:478–87. doi: 10.1111/j.1399-5618.2012.01033.x
10. Yüksel C, Öngür D. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biol Psychiatry.* (2010) 68:785–94. doi: 10.1016/j.biopsych.2010.06.016
11. Michael N, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B. Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychol Med.* (2003) 33:1277–84. doi: 10.1017/S0033291703007931
12. Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Archiv Gen Psychiatry.* (2007) 64:193–200. doi: 10.1001/archpsyc.64.2.193
13. Michael N, Erfurth A, Pfleiderer B. Michael N, Erfurth A, Pfleiderer B. Elevated metabolites within dorsolateral prefrontal cortex in rapid cycling bipolar disorder. *Psychiatry Res.* (2009) 172:78–81. doi: 10.1016/j.pscychresns.2009.01.002
14. Cecil KM, DelBello MP, Sellars MC, Strakowski SM. Proton magnetic resonance spectroscopy of the frontal lobe and cerebellar vermis in children with a mood disorder and a familial risk for bipolar disorders. *J Child Adolesc Psychopharmacol.* (2003) 13:545–55. doi: 10.1089/104454603322724931
15. Atagün MI, Sikoglu EM, Can SS, Ugurlu GK, Kaymak SU, Çayköylü A., et al. Neurochemical differences between bipolar disorder type I and II in superior temporal cortices: a proton magnetic resonance spectroscopy study. *J Affect Disord.* (2018) 235:15–19. doi: 10.1016/j.jad.2018.04.010
16. Pålsson E, Figueras C, Johansson AG, Ekman CJ, Hultman B, Östlind J., et al. Neurocognitive function in bipolar disorder: a comparison between bipolar I and II disorder and matched controls. *BMC Psychiatry.* (2013) 13:165. doi: 10.1186/1471-244X-13-165
17. Haroon E, Woolwine BJ, Chen X, Pace TW, Parekh S, Spivey JR., et al. IFN-alpha-induced cortical and subcortical glutamate changes assessed by magnetic resonance spectroscopy. *Neuropsychopharmacology.* (2014) 39:1777–85. doi: 10.1038/npp.2014.25
18. Fayed N, Andres E, Viguera L, Modrego PJ, Garcia-Campayo J. Higher glutamate+glutamine and reduction of N-acetylaspartate in posterior cingulate according to age range in patients with cognitive impairment and/or pain. *Acad Radiol.* (2014) 21:1211–7. doi: 10.1016/j.acra.2014.04.009
19. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* (2009) 65:732–41. doi: 10.1016/j.biopsych.2008.11.029
20. Guloksuz S, Cetin EA, Cetin T, Deniz G, Oral ET, Nutt DJ. Cytokine levels in euthymic bipolar patients. *J Affect Disord.* (2010) 126:458–62. doi: 10.1016/j.jad.2010.04.027
21. Fernandes BS, Steiner J, Molendijk ML, Dodd S, Nardin P, Gonçalves CA., et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry.* (2016) 3:1147–56. doi: 10.1016/S2215-0366(16)30370-4
22. Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL. Cytokines in bipolar disorder: paving the way for neuroprogression. *J Neural Plasticity.* (2014) 2014:360481. doi: 10.1155/2014/360481
23. Lotrich FE, Butters MA, Aizenstein H, Marron MM, Reynolds CF III, Gildengers AG. The relationship between interleukin-1 receptor antagonist and cognitive function in older adults with bipolar disorder. *Int J Geriatr Psychiatry.* (2014) 29:635–44. doi: 10.1002/gps.4048
24. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. *J Neuroinflam.* (2013) 10:43. doi: 10.1186/1742-2094-10-43
25. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). *Br J Psychiatry.* (2008) 192:52–8. doi: 10.1192/bjp.bp.106.032532
26. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* (1978) 133:429–35. doi: 10.1192/bjp.133.5.429

Conflict of Interest Statement: AY, AC, and JS: Employed by King's College London; Honorary Consultant SLaM (NHS UK); Paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders; No share holdings in pharmaceutical companies; Investigator initiated studies from AZ, Eli Lilly, Lundbeck, Wyeth; Grant funding (past and present): NIHR-BRC (UK); NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). CP is funded by the UK National Institute for Health Research (NIHR) Biomedical Research Center at the South London and Maudsley NHS Foundation Trust and King's College London, the UK Medical Research Council (grants MR/L014815/1, MR/J002739/1 and MR/N029488/1) and the Psychiatry Research Trust.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 28 March 2019
doi: 10.3389/fpsyt.2019.00145

Emotional Biases and Recurrence in Major Depressive Disorder. Results of 2.5 Years Follow-Up of Drug-Free Cohort Vulnerable for Recurrence

Henricus G. Ruhe[1,2,3]*, *Roel J. T. Mocking*[3], *Caroline A. Figueroa*[3,4], *Paulien W. J. Seeverens*[3], *Nessa Ikani*[1,5,6], *Anna Tyborowska*[1,2,6], *Michael Browning*[4], *Janna N. Vrijsen*[1,2,5], *Catherine J. Harmer*[4] and *Aart H. Schene*[1,2]

[1] Department of Psychiatry, Radboud University Medical Centre, Nijmegen, Netherlands, [2] Donders Institute for Brain, Cognition and Behavior, Radboud University, Nijmegen, Netherlands, [3] Department of Psychiatry, Location Academic Medical Center, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [4] Department of Psychiatry, University of Oxford, Oxford, United Kingdom, [5] ProPersona Mental Health Care, Depression Expertise Center, Nijmegen, Netherlands, [6] Department of Psychology, Behavioural Science Institute, Radboud University, Nijmegen, Netherlands

An interesting factor explaining recurrence risk in Major Depressive Disorder (MDD) may be neuropsychological functioning, i.e., processing of emotional stimuli/information. Negatively biased processing of emotional stimuli/information has been found in both acute and (inconclusively) remitted states of MDD, and may be causally related to recurrence of depression. We aimed to investigate self-referent, memory and interpretation biases in recurrently depressed patients in remission and relate these biases to recurrence. We included 69 remitted recurrent MDD-patients (rrMDD-patients), 35–65 years, with ≥2 episodes, voluntarily free of antidepressant maintenance therapy for at least 4 weeks. We tested self-referent biases with an emotional categorization task, bias in emotional memory by free recall of the emotion categorization task 15 min after completing it, and interpretation bias with a facial expression recognition task. We compared these participants with 43 never-depressed controls matched for age, sex and intelligence. We followed the rrMDD-patients for 2.5 years and assessed recurrent depressive episodes by structured interview. The rrMDD-patients showed biases toward emotionally negative stimuli, faster responses to negative self-relevant characteristics in the emotional categorization, better recognition of sad faces, worse recognition of neutral faces with more misclassifications as angry or disgusting faces and less misclassifications as neutral faces ($0.001 < p < 0.05$). Of these, the number of misclassifications as angry and the overall performance in the emotional memory task were significantly associated with the time to recurrence ($p \leq 0.04$), independent of residual symptoms and number of previous episodes. In a support vector machine data-driven model, prediction of recurrence-status could best be achieved (relative to observed recurrence-rate) with demographic and childhood adversity parameters (accuracy 78.1%; 1-sided $p = 0.002$); neuropsychological tests could not improve this prediction. Our data suggests a persisting (mood-incongruent) emotional bias when patients with recurrent depression are in remission. Moreover, these persisting biases might be mechanistically important for recurrence and prevention thereof.

Keywords: major depressive disorder, remission, relapse, recurrence, emotional bias, prediction

OPEN ACCESS

Edited by:
Gianluca Serafini,
Ospedale San Martino (IRCCS), Italy

Reviewed by:
Roland Zahn,
King's College London, United Kingdom
Yuping Ning,
Guangzhou Medical University, China

***Correspondence:**
Henricus G. Ruhe
eric.ruhe@radboudumc.nl;
h.g.ruhe@gmail.com

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *31 August 2018*
Accepted: *27 February 2019*
Published: *28 March 2019*

Citation:
Ruhe HG, Mocking RJT, Figueroa CA, Seeverens PWJ, Ikani N, Tyborowska A, Browning M, Vrijsen JN, Harmer CJ and Schene AH (2019) Emotional Biases and Recurrence in Major Depressive Disorder. Results of 2.5 Years Follow-Up of Drug-Free Cohort Vulnerable for Recurrence. Front. Psychiatry 10:145. doi: 10.3389/fpsyt.2019.00145

INTRODUCTION

Due to its high incidence, recurrence-rates and severity, Major Depressive Disorder (MDD) is a psychiatric disease which globally accounts for the greatest loss of years due to disability (1, 2). Defining predictors of recurrence that are preventable might help reduce this burden. The number of previous episodes of MDD is a strong predictor of both relapse and recurrence (1, 3, 4) —both are referred to as "recurrence" hereafter (5)– other predictors include the persistence of depressive symptoms (3) and coping style and/or daily hassles (1). However, in prior research, these predictors explained only ∼29% of variance of time to recurrence (6)(ten Doesschate, Bockting, Koeter, Schene, & DELTA Study Group, 2010).

An interesting additional factor explaining recurrence risk in MDD may be neuropsychological functioning, especially the processing of emotional stimuli/information. Negatively biased processing of emotional stimuli/information has been found in different cognitive domains, both in acute and remitted states. An example of negative biases in emotional processing is *attentional* biases for negative stimuli, which have also been repeatedly observed in acute MDD patients (7–9). This bias consists of selective attention for negative stimuli, such as sad faces (10). Altered emotional processing is interpreted as a failure to suppress attention for negative stimuli (11–13). Moreover, MDD patients lack a positive attentional bias that is normally observed in healthy individuals, and show a decreased response to pleasant stimuli (14, 15). Interestingly, this type of altered emotional processing is suggested to have clinical correlates: it is associated with an impeded recovery from depression (10, 16, 17). Based on such findings, biased processing of emotional information is currently regarded as an important contributor to the onset of depression, and may therefore also be causally related to recurrence of depression (13, 18–22). Moreover, in the acute stage, MDD patients have difficulties in retaining positive or neutral information to their working memory and in blocking and removing negative information from working memory (23–25).

While abundant evidence shows that acutely depressed individuals differ in emotional processing from non-depressed controls, referred to as mood-congruent biases, little is known about how individuals with recurrent MDD in remission differ from those controls (26–28). Analogous, biases when in remission of depression could be considered mood-incongruent. Some of the neuropsychological deficits seen during an acute episode of MDD seem to persist between episodes, and the level of neuropsychological impairment might even be related to the number of previous depressive episodes (29). This may indicate that, as opposed to representing a state, (i.e., characteristics are only seen during a depressive episode), altered emotional processing represents a trait in individuals with increased risk of developing a first or recurrent depressive episode. This is further substantiated by (1) the presence of negative bias in never-depressed relatives of depressed individuals (who are at high risk for MDD), for example children of depressed mothers (30–32); (2) the relationship between bias and symptomatic improvement over time (10); and (3) the association of negative bias with depression candidate genes (33, 34). Also, a negative information processing bias was observed in highly neurotic but never depressed individuals (35). Negative biases in emotional processing might result in more frequent dysphoric states, leading to emotional vulnerability under stress and ultimately to depressive feelings (36, 37).

Indeed, alterations in emotional processing have been observed in MDD patients in remission compared to healthy (never depressed) controls, although this evidence is limited (38). For example, the negative attentional bias observed in depressed persons may in a lesser form persist or be reactivated during a sad mood in remitted depressed individuals; although results are mixed (19, 39–45). Other biases in remitted patients concern the *negative interpretation* of neutral or ambiguous information (46), preferential recall of negative material (46–50), a *reduced error monitoring* due to prolonged emotional disturbance after self-monitored errors, decreased *learning* and a *ruminative thinking style* when confronted with negative information (13, 20). Moreover, cognitive effects seem to be greatest when emotional stimuli match the domain of greatest concern to the subject, e.g., represent self-referential information (51). However, the differences above have often only been observed when remitted depressed individuals are in a dysphoric mood or stressed, suggesting that these biases are activated by decreased mood (i.e., mood-congruent). In sum, evidence for the persistence of alterations in emotional processing (as a trait) during remission is not conclusive yet.

Importantly, the presence of neuropsychological differences between individuals vulnerable for recurrence of MDD and never-depressed controls does not necessarily imply that these neuropsychological processes are predictive of future recurrence. Until now only one study investigated the relation between self-referential emotional biases and recurrence (49). If such an association is replicated, alterations in emotional processing could be implicated to predict or recognize a preceding new episode at an early stage. Moreover, interventions to modify emotional processing biases have been developed for depressed individuals (37, 52–59). Therefore, if a relation between emotional biases and recurrence exists, this type of bias-modification intervention could also have a preventive effect in MDD patients in remission.

We therefore aimed to investigate self-referent, memory and interpretation biases in recurrently depressed patients in remission. To avoid any influence of medication on emotional processing (60), we only included participants who were voluntarily free of antidepressant maintenance therapy for at least 4 weeks. For the exploration of the different cognitive domains of altered emotional processing, we used tasks specifically designed to disentangle these. First, to test bias in self-referent information processing, we used an emotional categorization task (61). We presented positive and negative words describing a characteristic, and asked the subjects if they would appreciate this trait as desirable or undesirable. We hypothesized that subjects remitted from MDD would need less time to process negative trait words than controls and that shorter processing time would be associated with recurrence. Second, to explore possible bias in emotional memory we subjected the

remitted depressed individuals to a free recall of the emotion categorization task stimuli exactly 15 min after completing it (61). We hypothesized that subjects remitted from MDD would (1) remember more negative words than controls and (2) show more negative memory intrusions compared to never-depressed controls. We also expected the strength of the negative bias to be associated with recurrence and time to recurrence. Third, we used a facial expression recognition task (61), to test if alterations in recognition and reaction times would occur to faces with negative and positive expressions. We hypothesized that remitted MDD subjects would show (1) faster and better recognition of negative expressions compared to controls, (2) a slower recognition of positive expressions compared to controls, and (3) as in the previous task, that these effects would be associated with recurrence.

MATERIALS AND METHODS

Participants

We recruited patients with recurrent MDD currently in remission [$\leq$7 for $\geq$8 weeks on the Hamilton depression rating scale (HDRS) (62)] and not fulfilling the criteria for a current MDD episode–as assessed using the structured clinical interview for DSM-IV disorders [SCID-I (63) during inclusion]; between 35 and 65 years, with 2 or more MDD episodes according to the SCID-I. All participants gave written informed consent. The study was approved by the local Medical Ethics Committee of the Academic Medical Centre, Amsterdam, The Netherlands.

As described in our methods-paper (64), we recruited participants (and controls) via advertisements and via databases registering previous clinical treatment and/or participation in previous studies at the mood disorder department. In addition, we contacted patients with a known recurrent MDD without current medication through their general practitioners who have an affiliation with the Academic Medical Centre of Amsterdam (AMC).

Participants did not take psychopharmacologic drugs for at least 4 weeks, although we allowed incidental benzodiazepine use, as long as this could be stopped after informed consent. Exclusion criteria were current diagnosis of alcohol or drug dependence, psychotic or bipolar disorder, predominant anxiety disorder, electroconvulsive therapy within 2 months before assessment or a history of head trauma or neurological disease or severe general physical illness.

We likewise recruited never-depressed controls, free of lifetime psychopathology, throughout the study, who were matched on age ($\pm$3 years), sex and estimated intelligence (Dutch adult reading test (DART (65)); with a HDRS $\leq$7. Exclusion criteria for controls (as far as applicable) were identical to MDD-patients.

Clinical Assessment

After informed consent, we administered the SCID-I (63) to ascertain current and past depressive episodes, HDRS and IDS-SR (63) by phone interview, to ensure that participants did not meet criteria for a depressive episode, and—for the MDD group—were in remission. We thereafter scheduled a visit to our lab and requested participants to abstain from caffeinated drinks before performance of the tasks.

After instruction of the tasks and anthropomorphic measures, participants performed neuropsychological tasks in 2 blocks separated by a break. For description of the full baseline assessment see Mocking et al. (64).

Cognitive Tasks

Emotional Categorization (EmCAT)

In this task, 60 personality characteristics selected to be disagreeable or agreeable (i.e., valence) were presented on the computer screen for 500 ms each. The task lasted for 6 min [for a complete description of the task, see (66)]. Characteristics were translated from the original English version to Dutch (and back-translated), matched in terms of word length, ratings of usage frequency, and meaningfulness. Participants were asked to categorize the words as likable or dislikeable as quickly and accurately as possible. Specifically, they were asked to imagine whether they would be pleased or upset if they overheard someone else referring to them as possessing this characteristic, so that the judgment is self-relevant and in part (but deliberately less explicitly) self-referent than e.g., the self-referential encoding task (SRET) (67, 68). The emotional categorization task was followed by administration of the DART and a short break.

Emotional Memory Task (EmMem)

Exactly 15 min after completion of the emotional categorization task, participants were asked to recall as many personality characteristics as possible. The number of positive and negative words recalled was computed for correct and false responses. The aim of this task was to test if participants with recurrent MDD recalled more negative words and had more negative intrusions (recalling words that were not in the EmCAT) than the healthy control group.

Facial Expression Recognition Task (FERT)

Six basic emotions (happiness, surprise, sadness, fear, anger, disgust) from 10 different individuals from the Pictures of Facial Affect series (69), were morphed between each valence and neutral and presented in a random order for 500 ms, followed by a blank screen. Participants were instructed to respond as quickly as possible and indicate the emotion they recognized by pressing one of six designated keys on the keyboard. This task lasted for 20 min and has been extensively validated before (60, 61).

Follow-Up

We performed a follow-up of the recurrent MDD-participants by regular (every $\sim$4 months) phone-calls, during which the SCID and HDRS were administered (64). To maximize the detection rate of recurrences, we also instructed participants to contact us when they subjectively experienced a recurrence and informed a person close to them about these instructions.

Statistics

We used IBM's SPSS version 25.0 (SPSS Inc., Chicago IL, USA); we considered $p < 0.05$ as threshold for statistical significance. With power = 0.80 and two-tailed $\alpha = 0.05$, our sample size of 69 MDD-patients and 43 controls allowed us to detect effects with

a small effect size for ANOVA-based repeated measures analyses (>0.13) and moderate effect-sizes (>0.55) with independent *t*-tests (G*Power 3.1.9 Kiel, Germany). In case a patient or control did not complete a cognitive task, the subject was excluded for the analyses of that task. The computerized tasks prevented the occurrence of missing reaction times or accuracy when a task was completed.

Comparisons Between rrMDD-Patients and Controls

First, we calculated means for demographic and clinical variables. We assessed normality and compared baseline characteristics between patients and controls using independent samples *t*-test, χ^2 tests or Mann-Whitney U test for non-parametric data, as appropriate.

For the EmCAT, we first checked occurrence of outliers and extreme reaction times, and then calculated the mean accurate classifications and reaction times per subject. We first compared reaction times for accurate and inaccurate categorization of positive/negative characteristics using independent *T*-tests. For accurate responses, we investigate effects of valence and valence*group interactions with a repeated measures ANOVA. Finally, to investigate combined contrasts of positive/negative characteristics, accuracy and group (i.e., valence*group*accuracy interaction), we applied linear mixed models with group as a between-subject factor (patients, controls), emotional valence as a within-subject factor (negative characteristics vs. positive), accuracy (correct/incorrect) and reaction time as dependent variable.

For the EmMem a 2 × 2 × 2 repeated measures ANOVA was calculated, with group (patient, controls) as the between-subject factor and false vs. correct answers and positive vs. negative words as within-subject factors.

For the FERT we compared reaction times and (mis-)classifications between groups per valence with independent sample *t*-tests and the interactions of (mis-)classification*group with repeated measures ANOVA. We used a linear mixed model procedure with group as a between-subject factor (patient, controls) and emotional expression as a within-subject factor (angry, fearful, sad, disgusted, neutral, surprised and happy; grouped as negative, neutral and positive faces) with reaction time as the first outcome variable and accuracy as a secondly tested variable.

Associations With Recurrence

For associations with recurrence in remitted MDD-patients, in order to avoid circular associations and reduce the number of variables to be examined in association with recurrence risk, we used the significant differences and interactions with controls (previous section) to calculate outcome-specific composite scores (definitions provided in **Tables 4**, **5**). First, we compared baseline results of these outcomes for rrMDD-patients with and without a recurrence during prospective follow-up. Second, in order to take into account the time to the (depressive) event or censoring by loss to follow-up, we used Cox proportional hazards regression models, with time to first recurrence as primary outcome. Participants lost to follow-up or without relapse during follow-up were considered censored. Because the number of previous depressive episodes and residual depressive symptomatology have been established as independent predictors of recurrence (1, 3, 4), we included these variables in all models. As independent variables, we used the significant differences and interactions with controls (i.e., the outcome-specific composite scores). We used a forward stepwise inclusion of all independent variables for each task separately. Finally, we for each task, we developed a task-specific composite score by using all outcomes of a task in a logistic regression to predict whether a subject would be a rrMDD-patient or control. Of this prediction-model we saved the standardized residuals of each task per subject and used this as a composite score (i.e., representing the individual's deviation of the general model). These task-specific composite scores were then planned to be used in the Cox-models assessing the independent contributions of the emotional bias test-battery by (1) entering the three task-specific composite scores per task as separate predictors and (2) by entering the three task-based composite scores simultaneously.

Machine-Learning Approach to Predict Recurrence

Given the many outcome variables generated by the EmCAT, EmMem and FERT, the acknowledged multiple comparison problem when testing these in individual models and the risk of overfitting models with relatively few cases, we applied a data-driven machine-learning approach to investigate prediction of recurrence, irrespective of the patient-control comparison.

As described for predicting treatment-response by the same neurocognitive test-battery (70), a linear support vector machine (SVM) was used to combine demographic (extended with the Childhood Trauma Questionnaire (CTQ) (71, 72) questionnaire) and task features into binary predictions (i.e., recurrence/non-recurrence). SVMs are a widely used and robust method of deriving binary classifications, particularly when the ratio of data points to features is relatively low, like in this study. Analysis was performed using Matlab (version R2014b, Mathworks). Performance of the algorithm was assessed using a leave-one-out validation procedure during which a training set consisting of all but one participant was used. The training set was used for feature selection, estimation of the C- parameter and model training, with the left out sample being used solely for validation (73). Note that this approach results in variability in the features selected, the C-parameter used and the model weights for each iteration of the leave-one-out procedure. The value of the C-parameter used was selected based on the achieved accuracy within the training set using 50 values of the parameter ranging from 0.01 to 100. Feature selection was achieved by selecting the features with the highest area under the curve for predicting recurrence in the training set. Missing values of a given feature in either the training or testing set (e.g., reaction times for choices, which were not made by a particular participant could not be calculated) were entered as the mean value for that feature, calculated from the training set. The unbalanced nature of the data set (i.e., unequal numbers of recurrent and non-recurrent patients) was dealt with by setting the weight of each observation to 1/(number of observations of a given class) in the training set (74).

Separate analyses were completed to test the predictive ability of the emotional bias tasks, residual symptoms and previous

episodes, extended with childhood adversity (CTQ). Selection of variables/task features was independent of previous analyses. We then used different proportions of task features (10, 50, or 100% of available features). The rationale for assessing this range of proportions of task features is that, if most information about recurrence is contained in only a few task features then the classifier which uses just these features will perform better, whereas if information about recurrence is distributed throughout many task features, then the more inclusive classifiers will perform better. Significance ($p < 0.05$) of the classifier was determined based on accuracy relative to the *a-priori* recurrence rate in this sample (54.7%). We calculated the z-score for difference between proportions, and considered one-sided *p*-values, given the expected better performance of the classifier.

RESULTS

We included 73 remitted MDD-patients and 45 controls. Of these, 69 MDD-patients and 43 controls completed the neuropsychological test battery. Of the 69 MDD-patients, 64 (92.8%) had at least 1 follow-up measurement and 52 (75.4%) completed follow-up for 2.5 years (**Figure 1**).

The groups did not differ significantly on age, gender, intelligence score, education (75) and living situation (all $p > 0.05$; **Table 1**). However, remitted MDD-patients were significantly less often employed compared to controls ($p = 0.04$) and had a slightly but significantly higher HDRS-score than controls (Mann-Whitney; $p < 0.001$).

Baseline Measurements

EmCAT

We excluded 1 rrMDD-patient who did not complete the task. The EmCAT was performed correctly by most individuals: 35 of 68 rrMDD-patients and 22 of 43 controls had no inadequate responses to positively or negatively valenced characteristics. In direct groupwise-comparisons of reaction time for positive/negative characteristics and accuracy thereof,

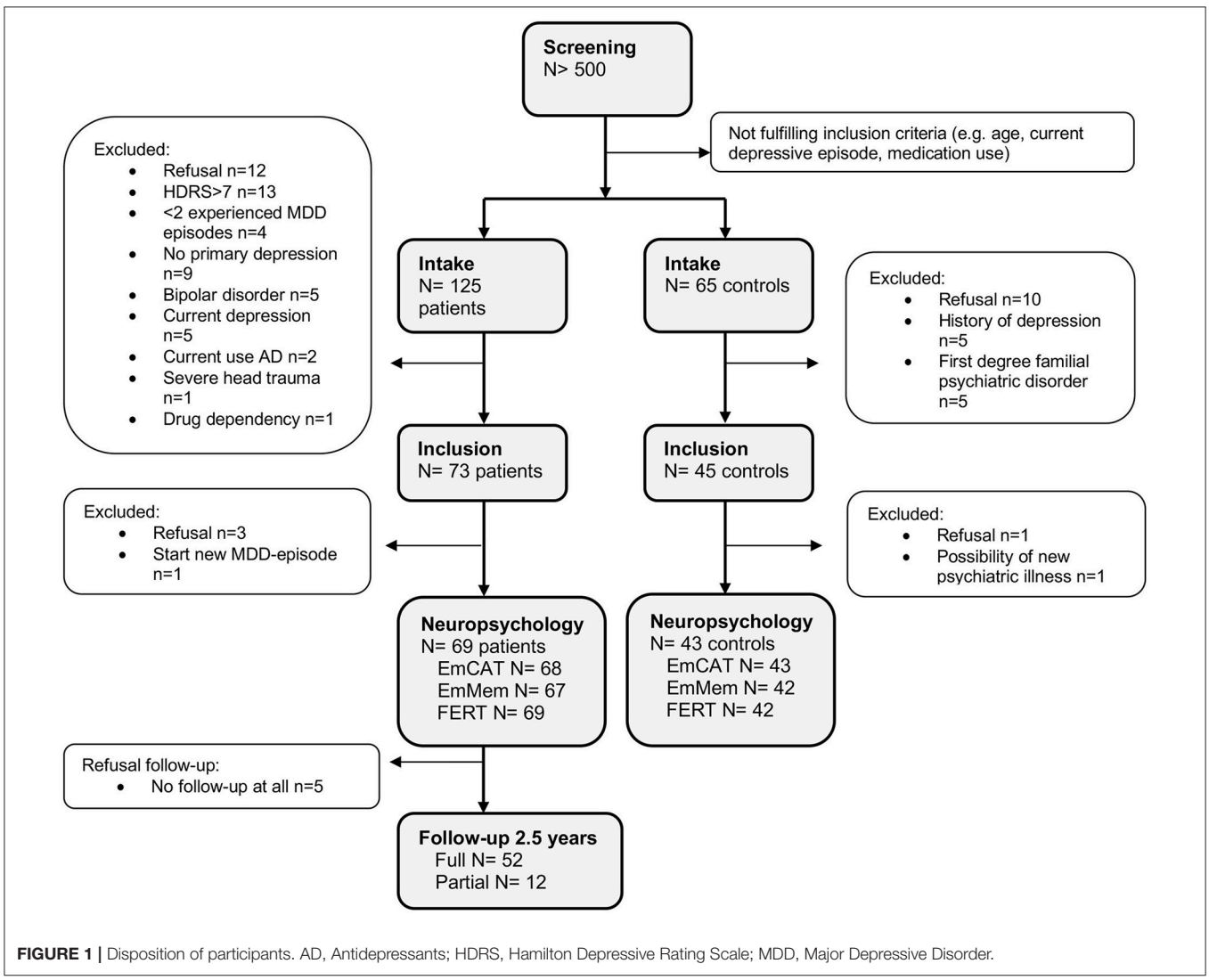

FIGURE 1 | Disposition of participants. AD, Antidepressants; HDRS, Hamilton Depressive Rating Scale; MDD, Major Depressive Disorder.

TABLE 1 | Remitted recurrent MDD patients vs. controls at baseline.

				Between-group statistics			
		rrMDD ($n = 69$)	**HC ($n = 43$)**	χ^2	***T***	***U***	***p***
Female	*N* (%)	45 (65.8%)	30 (69.8%)	0.25			0.68
Age	Years; mean (SD)	53.4 (7.7)	51.5 (8.2)		1.20		0.23
Education	Levels[a]	0/0/0/4/22/27/16	0/0/0/1/16/18/8	1.25			0.76
IQ	Mean (SD)	108.8 (8.2)	106.3 (9.6)		1.43		0.16
Living situation	Levels[b]	29/0/19/17/2/0/2	12/0/16/11/4/0/0	5.52			0.24
Employment status	Levels[c]	26/27/16/0	21/17/5/0	2.68			0.26
Currently employed	Yes (%)	46 (68.7)	37 (86.0)	4.28			0.04
Age of onset	Years; mean (SD)	26.7 (10.8)	–				–
Episodes	Median (IQR)						
last 10 years		2 (1–2)	–				–
lifetime		4 (2–7)					
HDRS	Median (IQR)	2 (0–5)	1 (0–1)			2,317	0.001
Childhood adversity (CTQ)	Mean (SD)						
Total		49.8 (14.4)	35.4 (12.7)		5.31		<0.001
Emot. abuse		11.6 (5.5)	6.9 (3.5)		5.47		<0.001
Phys. abuse		6.4 (2.8)	5.6 (1.7)		1.90		0.60
Sex. abuse		6.7 (3.1)	6.0 (3.0)		1.20		0.23
Emot. neglect		16.1 (5.3)	10.2 (4.3)		6.10		<0.001
Phys. neglect		8.9 (3.4)	6.7 (3.0)		3.32		0.001

CTQ, Childhood Trauma Questionnaire; HC, Healthy Control; HDRS, Hamilton Depression Rating Scale; rrMDD, remitted recurrent major depressive disorder; LEIDS-R, Leiden Index Depression Sensitivity-Revised; RRS, Ruminative Response Scale.

[a]Level of educational attainment (70): primary school not finished/primary school finished/primary school + ≤2 years of lower level secondary school finished/lower level secondary school finished/medium level secondary school finished/high level secondary school finished/pre-university or university degree).

[b]Living situation: alone/living with parents/cohabiting/cohabiting with children/single living with children/other/unknown.

[c]Employment status, low/middle/high/never worked; IQR, Inter-quartile range; χ^2, chi-square test statistic; p, p-value; U, Mann-Whitney U non-parametric test statistic; T, independent-samples T-test statistic.

only for misclassifications of negative characteristics rrMDD-patients had longer reaction times relative to controls (**Table 2**). When we restricted analyses to accurate responses, both rrMDD-patients and controls showed faster reaction times for, and better recognition of positive characteristics (significant main effect of valence; repeated measures ANOVA; [$F_{(1,109)} = 66.41$; $\eta^2 = 0.38$; $p < 0.001$] and [$F_{(1,109)} = 27.84$; $\eta^2 = 0.20$; $p < 0.001$], respectively). There were no significant differences between rrMDD-patients and controls, nor was there a significant group*valence interaction (all p's > 0.086). However, when we corrected for baseline differences in HDRS-scores between groups, for reaction times the group*valence interaction became significant [$F_{(1,107)} = 4.85$; $\eta^2 = 0.04$; $p = 0.03$], with patients being faster in negative and slower in positive characteristics, as compared to controls.

When we examined combined contrasts between positive/negative characteristics and groups in more sophisticated mixed models, regarding accuracy rrMDD made more mistakes (significant main effect of group; mixed model; [$F_{(1,4787.91)} = 3.91$; $p < 0.048$] and we observed more mistakes for negative characteristics (main effect for valence; [$F_{(1,4787.91)} = 39.62$; $p < 0.001$] without a group*valence interaction ($p = 0.56$). When we corrected for baseline differences in HDRS-scores between groups, significance of the difference between rrMDD and controls was lost ($p = 0.13$).

For the reaction times, we examined the valence*accuracy*group interaction. Overall reaction times were longer for incorrect responses (main effect for accuracy; mixed model; [$F_{(1,4265.28)} = 123.94$; $p < 0.001$]). Moreover, the accuracy*valence*group interaction was significant [$F_{(2,3810.45)} = 30.99$; $p < 0.001$). Relative to controls, rrMDD-patients were faster in response to negative characteristics and slower in response to positive characteristics, while especially for incorrect responses to positive characteristics this difference was the largest (**Figure 2**). When correcting for baseline differences in HDRS-scores between groups, results were similar, except that an overall slower response to positive relative to negative characteristics became significant [$F_{(1,4254.32)} = 4.48$; $p = 0.03$] too.

EmMem

We excluded 2 rrMDD-patients and 1 control who did not complete the task. In direct comparisons of patients and controls regarding separate outcomes we found no significant differences (**Table 2**). We examined the accuracy*valence*group interaction in the recall of positive and negative characteristics with a repeated measures ANOVA, also taking into account that participants falsely remembered positive/negative characteristics

TABLE 2 | Baseline comparisons of emotional biases in rrMDD vs. controls.

				Between-group statistics			
		rrMDD ($n = 69$)	**HC ($n = 43$)**	***T***	***F* (df)**	***U***	***p***
EMOTIONAL CATEGORIZATION (EmCat)§							
RT Neg. Acc.	ms (SEM)	1,084.3 (28.6)	1,110.6 (39.3)	0.551			0.58
RT Neg. Mis.*	ms (SEM)	1,246.0 (60.6)	1,036.9 (68.8)	−2.249			0.03
RT Pos. Acc.	ms (SEM)	980.2 (30.6)	950.2 (29.2)	−0.668			0.51
RT Pos. Mis.*	ms (SEM)	1,351.4 (127.1)	1,082.0 (152.4)	−1.329			0.19
Count Neg. Acc.	median (range)	28 (14)	28 (13)			1,432.5	0.85
Count Neg. Mis.	median (range)	2 (14)	2 (13)			1,491.5	0.85
Count Pos. Acc.	median (range)	29 (12)	29 (5)			1,598	0.38
Count Pos. Mis.	median (range)	1 (12)	1 (5)			1,326	0.38
EMOTIONAL MEMORY (EmMem)§							
Count Neg. Acc.	median (range)	3.0 (7)	3.0 (10)			1,473.5	0.67
Count Pos. Acc.	median (range)	3.0 (7)	3.0 (10)			1,479.5	0.65
Count Pos. New	median (range)	2.0 (9)	2.0 (8)			1,151.0	0.11
Count Neg. New	median (range)	1.0 (7)	1.0 (4)			1,394.5	0.93
FACIAL EMOTION RECOGNITION (FERT)§							
RT Angry	ms (SEM)	2,053.3 (62.5)	2,108.5 (123.7)	0.441			0.66
RT Fear	ms (SEM)	2,241.5 (63.7)	2,208.0 (82.0)	−0.322			0.75
RT Sad	ms (SEM)	2,440.6 (71.9)	2,314.4 (119.2)	−0.906			0.37
RT Disgust	ms (SEM)	2,179.1 (68.9)	2,303.8 (111.0)	0.954			0.34
RT Neutral	ms (SEM)	1,788.2 (71.2)	1,643.5 (87.1)	−1.274			0.21
RT Surprise	ms (SEM)	2,251.5 (60.8)	2,210.7 (95.7)	−0.379			0.71
RT Happy	ms (SEM)	1,754.9 (38.1)	1,700.7 (62.6)	−0.786			0.43
RT Negative	ms (SEM)	2,225.8 (37.1)	2,230.3 (47.4)		0.005 (1,415)		0.94
RT Positive	ms (SEM)	1,871.9 (39.3)	1,820.8 (50.0)		0.654 (1,154)		0.42

*As not all subjects misclassified characteristics during emotional categorization, these mean reaction-times are based on less subjects.

§Due to missing tasks for the EmCAT n = 68 rrMDD and 43 controls, for the EmMem n = 67 rrMDD and 42 controls, and for the FERT n = 69 rrMDD and 42 controls.

(**Figure 3**). Both in rrMDD-patients and controls, we found a better recall of positive characteristics (main effect of valence; $[F_{(1,107)} = 26.65;\ \eta^2 = 0.20;\ p < 0.001]$) and overall more characteristics were correctly remembered (main effect of accuracy; $[F_{(1,107)} = 46.00; \eta^2 = 0.30; p < 0.001]$). In addition, we found a significant accuracy*valence interaction (no difference between positive and negative characteristics when recalled correctly, but more positive than negative characteristics when recalled incorrect; $[F_{(1,107)} = 19.08;\ \eta^2 = 0.15;\ p < 0.001]$). However, there was no significant accuracy*valence*group interaction ($p = 0.24$). Correction for baseline HDRS differences between groups did not change these findings.

FERT

We excluded 1 rrMDD-patient who did not complete the task. Remitted rMDD-patients showed no differences in reaction times to any type of emotion (**Table 2**; independent *t*-tests, all *p*'s > 0.21; **Figure 4**). However, as shown in **Figure 5**, rrMDD-patients showed an increased recognition of sad faces, and more often misclassified stimuli as angry and disgusting (independent *t*-tests; $[t_{(108)} = 2.01;\ p = 0.047]$, $[t_{(108)} = 2.14;\ p = 0.035]$ and $[t_{(108)} = 1.98;\ p = 0.050]$, respectively). Relative to controls, rrMDD-patients recognized neutral faces less well (independent *t*-test; $[t_{(108)} = 2.49;\ p = 0.014]$, while they misclassified emotional faces less often as neutral (independent *t*-test; $[t_{(108)} = 2.96;\ p = 0.004]$. Only for neutral faces there was a significant (mis-)classification*group interaction (repeated measures ANOVA; $[F_{(1,108)} = 8.33;\ \eta^2 = 0.07;\ p = 0.005]$. These findings did not change when we corrected for differences in HDRS between groups.

Next, we combined angry, fear, sad and disgusting expressions as negative faces, and surprised and happy as positive faces. When examining reaction times to positive or negative faces in a linear mixed model, we found no differences between rrMDD-patients and controls (main effect of group; $p = 0.595$), and in both groups a significant faster responses to positive than negative faces (main effect of valence; linear mixed model; $[F_{(1,428.00)} = 75.98;\ p < 0.001]$) without a valence*group interaction ($p = 0.526$; **Figure 4**). Comparisons of neutral with positive or negative faces, only showed significant slower reaction-times for negative and positive, relative to neutral faces ($[F_{(1,173.83)} = 63.56;\ p < 0.001]$ and $[F_{(1,174.41)} = 4.03;\ p = 0.046]$, respectively), without a significant main group effect or valence*group interaction ($p > 0.248$; **Figure 4**).

For accuracy, using the same categorization, for positive vs. negative faces we observed better accuracy in rrMDD than in

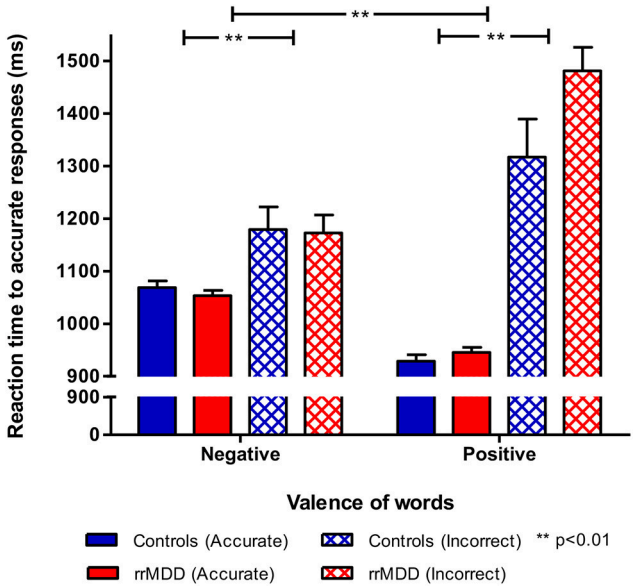

FIGURE 2 | Reaction times by accuracy in rrMDD-patients and controls for the emotional categorization task. Figure shows reaction times of rrMDD patients vs. controls, distinguishing responses that are accurate positive/negative or inadequate. In a mixed model reaction times were slower for incorrect responses (main effect for accuracy; $p < 0.001$) and the accuracy*valence*group interaction was significant ($p < 0.001$). Relative to controls, rrMDD-patients were faster in response to negative characteristics and slower in response to positive characteristics, while especially for incorrect responses to characteristics words this difference was the largest. $^{**}p < 0.01$; rrMDD, remitted recurrent depressive disorder.

controls (main effect of group; linear mixed model; [$F_{(1,471.71)} = 6.45$; $p = 0.011$]), better accuracy for positive vs. negative faces (main effect of valence; [$F_{(1,471.71)} = 144.47$; $p < 0.001$]) without a valence*group interaction ($p = 0.765$; **Figure 6**). For the accuracy of classifications as positive or negative vs. neutral, in general, positive or negative faces were better classified than neutral (main effect of valence; linear mixed model; all p's < 0.001), with a significant valence*group interaction (worse classification of neutral faces by rrMDD and better classification of positive and negative faces by rrMDD; [$F_{(1,264.55)} = 5.82$; $p = 0.017$] and [$F_{(1,533.90)} = 9.54$; $p = 0.002$], respectively).

For misclassifications of facial expressions, all subjects misclassified faces more often as negative than positive (main effect of valence; linear mixed model; [$F_{(1,346.85)} = 60.31$; $p < 0.001$]), without a significant difference between groups or valence*group interaction (both p's > 0.077). For neutral vs. negative faces, we observed less misclassifications by rrMDD (main effect of group; [$F_{(1,113.91)} = 7.01$; $p = 0.009$]), more misclassifications as neutral (main effect of valence; [$F_{(1,113.91)} = 786.75$; $p < 0.001$) which was driven by rrMDD-patients having less misclassifications as neutral and more misclassifications as negative (significant valence*group interaction; [$F_{(1,113.91)} = 10.23$; $p = 0.002$]). Likewise, for positive vs. neutral, we observed significantly less misclassifications by rrMDD (main effect of group; [$F_{(1,114.08)} = 9.35$; $p = 0.003$]), more misclassifications as neutral (main effect of valence; [$F_{(1,114.08)} = 890.14$; $p < 0.001$]) again driven by less misclassifications as neutral in rrMDD but with a comparable number of misclassifications as positive between rrMDD-patients and controls (significant valence*group interaction; [$F_{(1,114.08)} = 7.76$; $p = 0.006$]; **Figure 6**).

Follow-Up and Associations With Recurrence

Of the 64 MDD-patients who had at least 1 follow-up measurement, 35 (54.7%) had a recurrence, within a median period of 233 days (IQR 92-461). Patients with a recurrence had a younger age of onset (Independent T-Test; $p = 0.035$), more previous episodes in the last 10 years (Mann-Whitney; $p = 0.001$) but did not differ with respect to residual symptoms ($p = 0.85$; **Table 3**).

In the comparison of baseline results of rrMDD-patients without vs. those with a recurrence, we used significant comparisons and interactions with controls from **Table 2** to calculate outcome-specific composite scores. Patients with a recurrence during follow-up significantly more often misclassified faces as angry than resilient patients (Mann-Whitney; $p = 0.037$), all other comparisons were not significant ($p > 0.17$; **Table 4**).

Second, examining associations with recurrence in Cox-proportional hazard models (all correcting for residual symptoms and previous episodes in the last 10 years), we found that only the misclassification of faces as angry in the FERT was significantly associated with time to recurrence (Wald = 5.52; $p = 0.019$). Of the a priori defined task-based composite scores only the standardized residuals of the EmMem was significantly associated with time to recurrence (Wald = 4.21; $p = 0.040$). The planned combinations of task-based composite scores were not significantly associated with recurrence.

Support Vector Machine Classifiers to Predict Recurrence

The accuracies and sensitivity/specificity of different classifiers are displayed in **Table 6**. In the table we show how different combinations of neuropsychological tasks and demographic information (number of previous episodes in last 10 years, residual symptomatology, age and gender, also extended with CTQ-scores) perform when different percentages of available features are selected. The best classifier had a significantly better accuracy of 78.1% relative to the *a-priori* recurrence rate in the sample of this study (54.7%) (EmCAT + EmMem + demographic/CTQ data; 10% features; $z = 2.8$; 1-sided $p = 0.002$). However, when inspecting the 4 predicting parameters in this SVM-outcome, these were only demographic/CTQ-items (number of previous episodes in last 10 years, age of onset, CTQ-physical abuse subscale-score and CTQ-physical abuse ≥ 8). Moreover, when running the SVM on the extended demographic predictor set only, a 50% features solution (containing age, number of previous episodes in last 10 years, age of onset, CTQ-emotional abuse, CTQ-physical abuse, CTQ-emotional neglect subscale-scores, CTQ-total score, CTQ-physical abuse ≥ 8 and CTQ-emotional neglect ≥ 15)

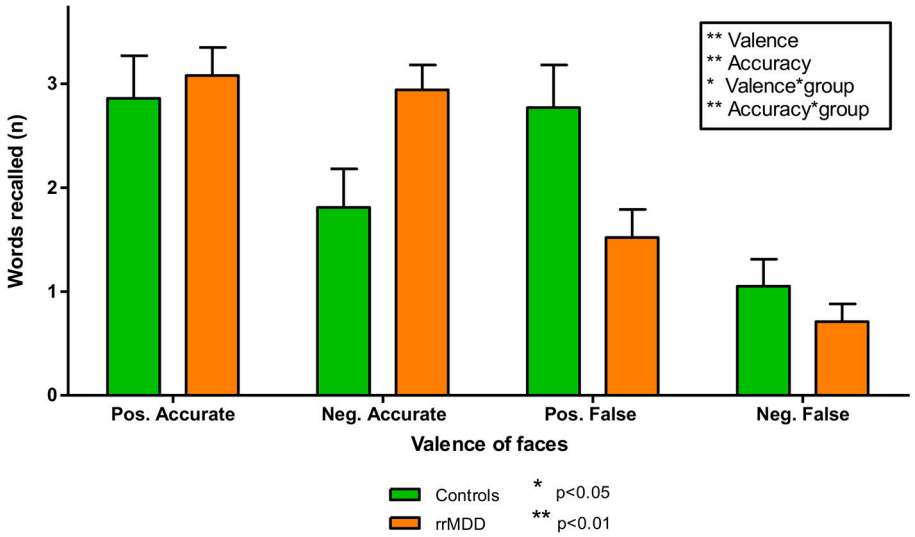

FIGURE 3 | Accurately and falsely endorsed characteristics in rrMDD-patients and controls for the emotional memory task. Figure shows the number of characteristics reported by rrMDD patients vs. controls, distinguishing characteristics that are accurately or falsely endorsed. In a repeated measures ANOVA, we found significant main effects for valence (better recall of positive characteristics; $p < 0.001$) and accuracy (overall more characteristics were correctly endorsed; $p < 0.001$), with a significant accuracy*valence interaction (no difference between positive and negative characteristics when recalled correctly, but more positive than negative characteristics when recalled incorrect; $p < 0.001$). However, the accuracy*valence*group interaction was not significant ($p = 0.24$). *$p < 0.05$; **$p < 0.01$; rrMDD, remitted recurrent depressive disorder.

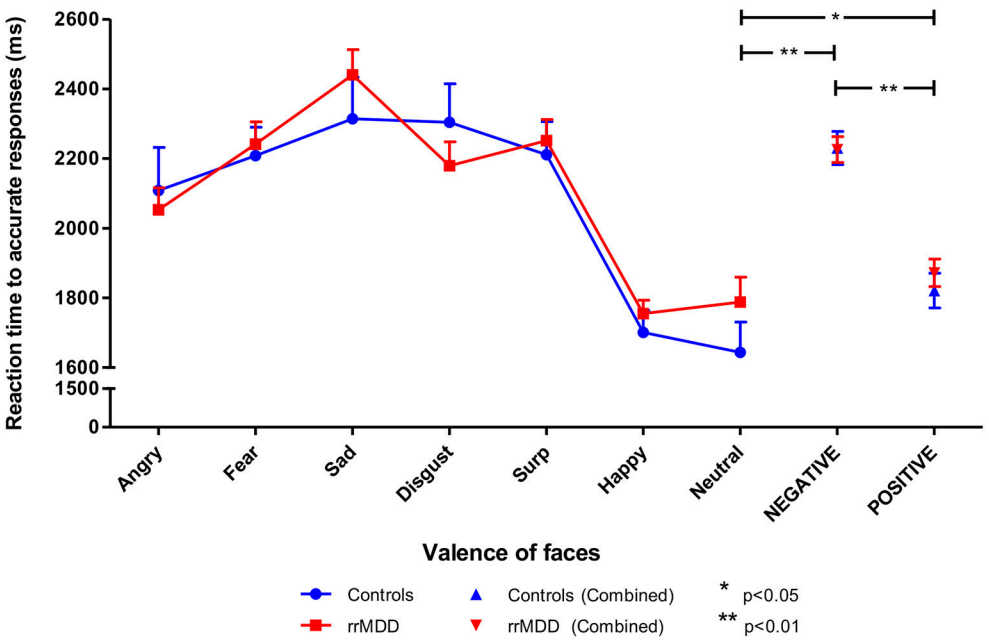

FIGURE 4 | Reaction times in rrMDD-patients and controls when performing the facial expression recognition task. Figure shows the reaction times to emotional expressions (irrespective of accuracy of recognition) in rrMDD-patients and controls. At the right, the valences angry, fear, sad and disgust are combined as negative, while surprise and happy are combined as positive emotions. There were no differences in reaction-time between rrMDD-patients and controls for any emotion. There was a significant main effect of valence ($p < 0.001$), with significant slower reaction-times for negative ($p < 0.001$) and positive ($p = 0.046$), relative to neutral faces, but without a significant main group effect or valence*group interaction ($p > 0.248$).*$p < 0.05$; **$p < 0.01$; rrMDD, remitted recurrent depressive disorder.

provided approximately the same predictive accuracy (75.0%; $z = 2.4$; 1-sided $p = 0.008$). The best model containing neuropsychological features approximating this result was the FERT + demographics/CTQ (10% features) classifier (containing number of previous episodes in last 10 years, age of onset, CTQ-physical abuse subscale-score, FERT misclassifications as

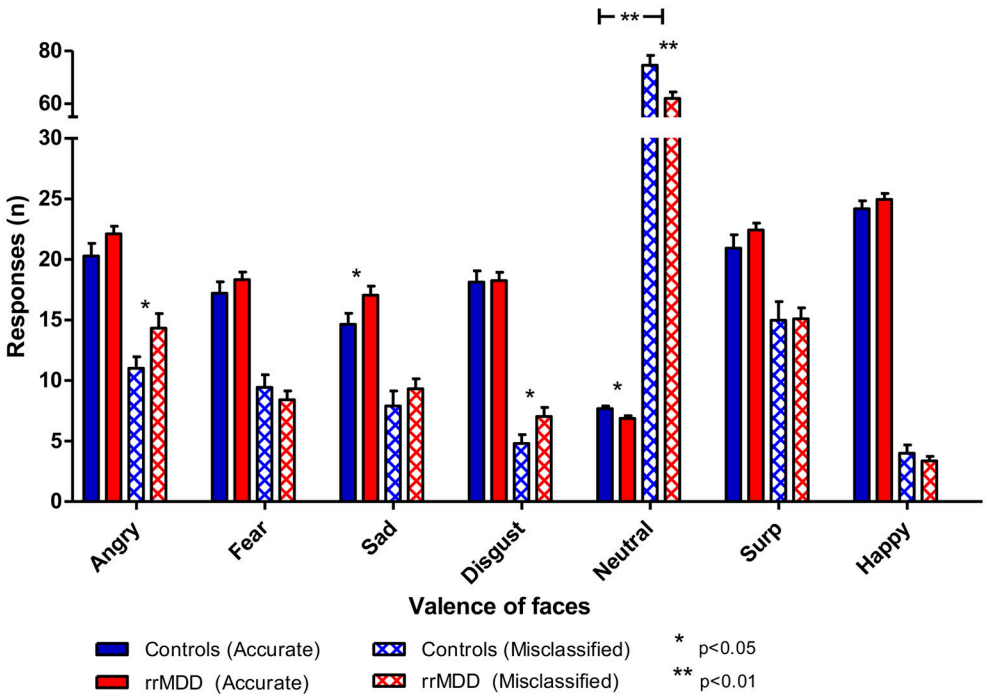

FIGURE 5 | Accuracy of recognition of 7 valences of facial expressions by rrMDD-patients vs. controls for the facial expression recognition task. Figure shows the number of emotional expressions (7 valences) accurately recognized and misclassified as the indicated emotion for rrMDD-patients and controls. There was an increased recognition of sad faces (p=0.047), higher misclassification as angry (p=0.048) and disgusting (p=0.046), worse recognition of neutral faces (p=0.005) and less misclassifications as neutral (p=0.003) by rrMDD vs. controls. For neutral faces there was a significant (mis-)classification*group interaction (p=0.005). * p<0.05; ** p<0.01; rrMDD, remitted recurrent depressive disorder.

angry and FERT misclassifications as negative; 70.3%; $z = 1.8$; 1-sided $p = 0.034$).

DISCUSSION

We assessed biased processing of emotional material in different cognitive domains (i.e., self-referent, emotional memory and interpretation biases) in a drug-free remitted recurrently depressed sample. We found that rrMDD-patients show biases toward emotionally negative stimuli (i.e., faster responses to negative self-relevant characteristics, better recognition of sad faces, worse recognition of neutral faces with more misclassifications as angry or disgusting faces and less misclassifications as neutral faces), of which the number of misclassifications as angry and the overall performance in the emotional memory task were also associated with the time to recurrence during 2.5 years of follow-up. In data-driven SVM classifiers, especially demographic and childhood adversity parameters, but also combined with misclassifications as angry/negative faces showed significant better prediction of recurrence-status. Overall, our data suggests persisting emotional biases when patients with recurrent depression are in remission, which are -at least partly- prospectively associated with recurrence.

Negative biases have been repeatedly observed in acutely depressed individuals, while findings in remitted or high-risk groups have been mixed (7, 76). Moreover, the associations with new episodes have been investigated less (49, 76), and only for self-referent biases. Below we will discuss our findings for different aspects of the biases we investigated in this study.

Bias in Self-Relevant Material (EmCAT)

With the mixed model analyses of the emotional categorization task, enabling the investigation of combinations of positive/negative characteristics and accuracy, we found a bias in self-relevant information processing: first, rrMDD-patients generally made more mistakes in adequately recognizing positive or negative characteristics than controls; second, in line with our hypothesis, relative to controls, rrMDD-patients were faster in response to negative characteristics and slower in response to positive characteristics, while especially for incorrect responses to positive characteristics this difference was the largest. However, contrary to our hypothesis, the reaction times to negative or positive characteristics separately or in combination (mean reaction-time negative–mean reaction time positive) were not associated with recurrence-risk over 2.5 years.

It has been proposed by earlier research, that a lack of a protective positivity bias observed in depressed individuals might be another component of depression existing independently from a negativity bias (76). In contrast to depressed individuals,

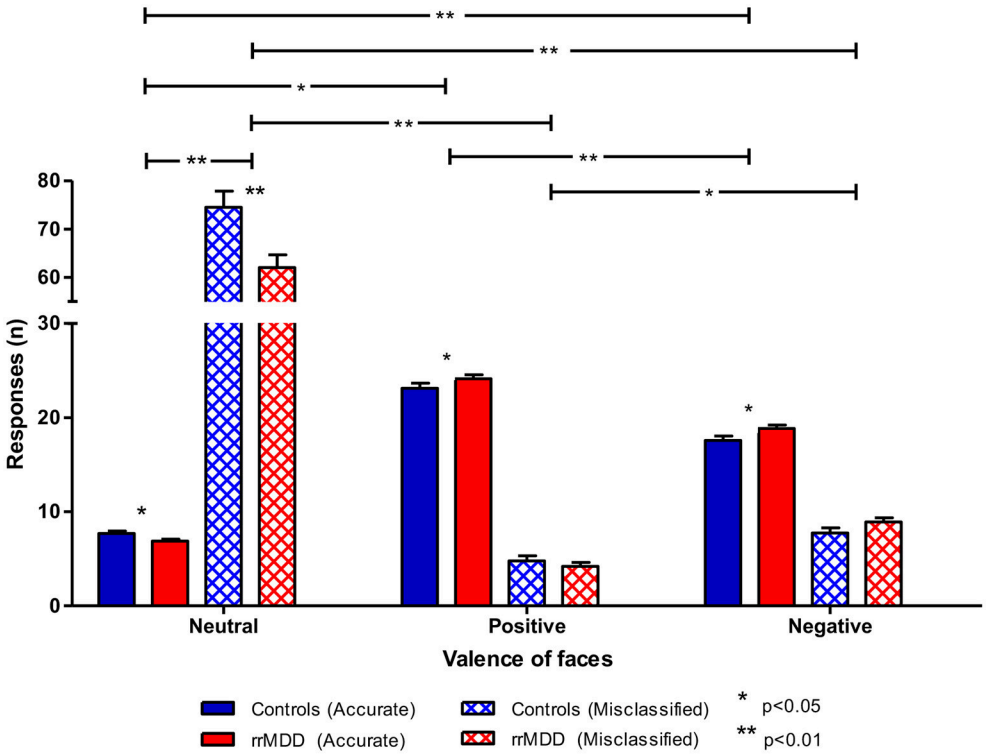

FIGURE 6 | Accuracy of recognition of neutral vs. positive/negative facial expressions by rrMDD-patients vs. controls for the facial expression recognition task. Figure shows the number of emotional expressions (neutral vs. positive vs. negative) accurately recognized and misclassified as the indicated emotion for rrMDD-patients and controls. For accurate responses, for positive vs. negative faces we found significant main effects for group ($p = 0.011$), for positive or negative vs. neutral, there was a significant main effect for valence (better classification of positive or negative than neutral faces; $p < 0.001$), with a valence*group interaction [positive ($p = 0.017$); negative ($p = 0.002$)]. For misclassifications, for positive vs. negative faces we found significant main effects for valence ($p = 0.011$); for negative vs. neutral, there was a significant main effect for group ($p = 0.009$), valence ($p < 0.001$) and the valence*group interaction ($p = 0.002$); for positive vs. neutral, there was a main effect for group ($p = 0.003$), valence ($p < 0.001$) and the valence*group interaction ($p = 0.006$).* $p < 0.05$; ** $p < 0.01$; rrMDD, remitted recurrent depressive disorder.

euthymic healthy individuals appeared to have a positive attentional bias, in contrast to depressed individuals, who may often lack such a "protective" bias (14). Since we investigated euthymic subjects who were previously depressed, our valence*group*accuracy interaction is indicative of both increases in negative and decrease of positive self-relevant bias in rrMDD-patients, which is different from controls (i.e., rrMDD-patients have a negative bias and lack a protective bias). Nevertheless, in the current sample, the difference between reaction times to accurately identified negative and positive characteristics was not associated with recurrence.

Negative biases in self-referent material have been found in remitted MDD patients vs. controls before, e.g., when using the SRET (77). In a recent study by LeMoult et al. euthymic female individuals with a history of depression exhibited negatively biased self-referential processing (less positive and more negative words endorsed) during the SRET, however assessed *after* a negative mood induction (49). The latent SRET variable (additionally including memory of negative words) was found to prospectively predict episode recurrence over 3 years of follow-up (49).

Methodological differences might explain the discrepancy between our and these findings. First, the use of a mood induction in this study might have increased the negative biases in participants, in line with the cognitive reactivity model, and may have probed the vulnerability for recurrence. This would imply that self-referent biases might be latent in remission and mood-congruent only, instead of persistently present independent of mood-state. If so, we might have observed a negative bias if we would have applied a mood-induction before the EmCAT. Second the difference in SRET vs. the EMCAT task (explicitly referring to oneself vs. valence of characteristics in relation to oneself; i.e., self-referent vs. self-relevant/partly self-referent) might have influenced the variability of correct responses, since most subjects determined the right valence for most characteristics in the EmCAT. This might have reduced the possibility to find associations with recurrence and EmCAT outcomes. Next, the approach of summarizing the outcomes of the SRET, including the memory in one latent SRET-measure as predictor of recurrence (49) might also explain the different findings since combination of information might increase sensitivity to detect biases. Finally, in our non-mood-induced EmCAT, we found most

TABLE 3 | Baseline characteristics of rrMDD patients recurrent vs. resilient during follow-up.

				Between-group statistics			
		Recurrence ($n = 35$)	**Resilient ($n = 29$)**	χ^2	***T***	***U***	***p***
Female	*N* (%)	25 (71.4%)	19 (65.5%)	0.26			0.61
Age	Years; mean (SD)	52.8 (7.1)	54.7 (8.6)		0.98		0.37
Education	Levels[a]	0/0/0/2/15/13/5	0/0/0/2/6/12/9	4.52			0.21
IQ	Mean (SD)	108.0 (7.5)	110.0 (9.5)		0.90		0.37
Living situation	Levels[b]	15/0/9/7/2/0/2	11/0/9/9/0/0/0	4.34			0.40
Employment status	Levels[c]	15/15/5/0	9/10/10/0	3.64			0.16
Currently employed	Yes (%)	22 (64.7)	20 (71.4)	0.32			0.60
Age of onset	Years; mean (SD)	24.2 (10.7)	30.1 (11.0)		2.16		0.04
Episodes	Median (IQR)						
last 10 years		2 (1–3)	1 (1–2)			746	0.01
lifetime		4 (2–12.5)	5 (2–5.5)			606	0.18
HDRS	Median (IQR)	2 (1–5)	2 (0–4.5)			521	0.85
Childhood adversity (CTQ)	Mean (SD)						
Total		52.0 (15.5)	45.6 (11.5)		1.78		0.08
Emot. abuse		12.1 (5.8)	10.3 (4.8)		1.33		0.19
Phys. abuse		7.0 (2.9)	5.4 (1.2)		2.93		0.005
Sex. abuse		6.9 (3.2)	6.7 (3.1)		0.36		0.72
Emot. neglect		17.0 (5.5)	14.7 (4.9)		1.76		0.08
Phys. neglect		8.9 (3.4)	8.3 (3.1)		0.74		0.47

Legend see ***Table 1***.

robust interactions regarding reaction times, which could not be modeled by LeMoult et al. (49). Again, although we did not find associations with recurrence, differences in reaction times might have been more sensitive to predict recurrence when obtained after a mood-induction (expected to increase the differences in reaction times between positive and negative adjectives).

Bias in Memory of Emotional Material (EmMem)

In contrast with our hypotheses, bias in emotional memory was not different between rrMDD-patients and controls. In the emotional memory task, we only found better recall of positive words, with more words remembered correctly than incorrectly and a significant accuracy*valence interaction (no difference between positive and negative words when recalled correctly, but more positive than negative words when recalled incorrectly). Interestingly, despite the absence of significant differences between rrMDD-patients and controls on separate outcome variables, the task-based composite score (indicating the individual's deviation of the general pattern of differences between patients and controls) was associated with recurrence.

In previous studies, recall of negative words was increased in rrMDD in investigations with the SRET (49, 77), which was accompanied by unexpected recall afterwards. In addition Vrijsen et al. also reported increased negative memory bias for negative stimuli in remitted MDD after a sad mood induction, which was not specifically associated with having recurrent MDD (48). Interestingly, Gethin and colleagues reported that reductions in positivity bias in a comparable sample of remitted MDD-patients were only found in subjects reporting early life stress (47). In *post-hoc* analyses, approximating the analyses by Gethin et al. we did not find evidence for an effect of early life stress [assessed by the CTQ (71, 72)] on reductions of recall of positive (relative to negative) words in our sample (results available on request). As noted above, LeMoult et al. reported an association with recurrence of the SRET-results, containing a variable for memory of negative words (49). Given the fact that our task-based composite score is relative to the present control sample, the association with prospective recurrence is interesting but will need replication and preferably must be substituted by an absolute value independent of a control sample.

The mood induction before, and the shorter time between the SRET and recall (3 min) (49) compared to this study (no mood-induction; time between ECAT and recall 15 min) might both be relevant factors that might have reduced variability between subjects in our study; these in turn might have obscured associations between memory bias and recurrence. Moreover, it has been suggested that the level of self-reference of the presented characteristics and/or the overgeneralization of autobiographical memories (i.e., reduced ability to recall specific autobiographical memories) are more important in the inability of rrMDD subjects to be resilient against recurrence (76, 78). Unfortunately, we did not test autobiographical memories in addition to the EmCAT/EmMem.

TABLE 4 | Baseline emotional biases (expressed as outcome-specific composite scores) in rrMDD patients recurrent vs. resilient during follow-up.

				Between-group statistics		
		Recurrent (*n* = 35)	**Resilient (*n* = 29)**	***T***	***U***	***p***
Emotional Categorization (EmCat)						
Positive Mis. + Negative Mis.	*n* (SEM)	3.8 (0.65)	4.4 (0.68)		445	0.39
RT Neg. – RT Pos. Acc.	ms (SEM)	114.5 (27.45)	92.4 (23.22)		609	0.17
RT Neg. – RT Pos. Mis.*	ms (SEM)	−87.5 (173.17)	−198.9 (179.22)	−0.45		0.66
Emotional Memory (EmMem)						
Negative Acc. – Positive Acc.	n (SEM)	−0.14 (0.36)	0.00 (0.32	0.29		0.78
Negative Mis. – Positive Mis.	n (SEM)	−1.20 (0.35)	−0.79 (0.43)		518.5	0.69
Positive Acc. – Positive Mis.	n (SEM)	1.09 (0.56)	1.29 (0.29)	0.32		0.75
Negative Acc. – Negative Mis.	n (SEM)	2.14 (0.38)	2.07 (0.47)		471.5	0.80
(Negative Mis. – Positive Mis.)/(Positive Acc. – Negative Acc)§	% (SEM)	−54.5 (41.2)	−4.6 (44.8)		250.5	0.25
Facial Emotion Recognition (FERT)						
Sad Acc.	n (SEM)	16.7 (1.13)	16.9 (1.22)	0.89		0.93
Neutral Acc.	n (SEM)	6.5 (0.34)	7.2 (0.36)	1.41		0.69
Angry Mis.	n (SEM)	16.1 (1.85)	11.1 (1.46)		662	**0.04**
Disgust Mis.	n (SEM)	7.0 (1.08)	6.6 (0.98)		513.5	0.94
Neutral Mis.	n (SEM)	60.6 (3.59)	62.9 (3.89)	0.45		0.66
Positive Acc. – Neutral Acc.	n (SEM)	40.3 (1.25)	38.8 (1.88)	−0.65		0.52
Negative Acc. – Neutral Acc.	n (SEM)	67.4 (2.85)	67.7 (3.33)	0.06		0.95
Negative Mis. – Neutral Mis.	n (SEM)	−17.9 (6.06)	−28.9 (5.60)	−1.31		0.19
Neutral Mis. – Positive Mis.	n (SEM)	41.7 (3.78)	45.0 (4.57)	0.55		0.58

*Outcome-specific composite scores were defined based on significant differences and interactions of outcomes between patients and controls (see **Table 2**).*

**As not all subjects misclassified characteristics during emotional categorization, these mean reaction-times are based on less subjects (16 with recurrence and 16 resilient).*

§Cases with Positive Acc. – Negative Acc = 0 omitted from analyses (7 recurrent /7 resilient).

Bold value indicate significance at $p < 0.05$.

Bias in Recognition of Faces (FERT)

In the facial expression recognition task, contrary to our hypotheses for reaction times, there were no overall or valence -specific differences in reaction times between groups. However, in line with our hypothesis of bias toward negatively valenced faces, rrMDD-patients better recognized sad faces, more often misclassified stimuli as angry and disgusting and exhibited poorer recognition of neutral faces than controls. Further, they misclassified emotional faces less often as neutral. Moreover, in interaction analyses, rrMDD-patients showed worse classification of neutral faces and better classification of positive and negative faces. This was complemented by less misclassifications as neutral but more misclassifications as negative (and comparable misclassifications as positive) faces by rrMDD-patients vs. controls. Of these findings, only the increased misclassification of faces as angry was significantly associated with time to recurrence during 2.5 years of follow-up. This finding was corroborated by the SVM classifier that included the FERT-outcomes and revealed a significant classification with 50% of the features.

Depressed patients show mood-congruent biases in the identification of facial expressions of emotion (76, 79, 80). In line with our findings, earlier research described that these biases in the identification of facial expressions of emotion appear to remain after recovery from a depressive episode (41, 45, 81). Joorman et al. (45) showed that formerly depressed participants selectively attended sad faces, while controls selectively avoided sad faces and oriented toward happy faces instead, indicative of a positive bias that was not observed in remitted MDD-patients. Leppanen et al. (41) used neutral, happy and sad faces only, and found in their analyses of remitted MDD-patients vs. controls that these patients misclassified neutral faces more often (and equally) as either sad or happy, while we found more misclassifications (from either valence) as angry in rMDD, but -comparably- identified worse recognition of neutral faces by rrMDD. LeMoult et al. (81) also used a different task (with computer-morphed variable intensity of emotions) while also including a mood induction procedure: they observed differences in recognition of happy emotions while we found an increased recognition of sad and more misclassification as angry faces. Unfortunately, LeMoult et al. did not report the misclassifications as angry and neither of these two studies performed a follow-up to associate biases with recurrence (41, 81).

We expect that our and Leppanen et al.'s non-mood-induced results point to a trait-like difficulty in recognizing neutral expressions, presumably as they see them as more negative, while the mood-induction used by LeMoult might have elicited mood-congruent (state-like) recognition/interpretation biases (41, 81). The finding that misclassifications were significantly more often toward angry faces could be hypothesized as representation of implicit expectations/anxiety of having done something wrong, i.e., self-blame as proposed by Zahn et al.

TABLE 5 | Cox proportional hazards models.

	Unit	Exp(B)	95% CI	*p* (Wald)	*p* (model)
Emotional Categorization (EmCat)					
Previous episodes−10 years	*n*	*1.119*	*1.042–1.203*	*0.002*	
HDRS-score residual symptoms	*1 point*	*1.014*	*0.880–1.168*	*0.849*	*0.003*
Positive Mis. + Negative Mis.	n	0.970	0.871–1.080	0.567	
RT Neg. – RT Pos. Acc.	10 ms	1.013	0.986–1.041	0.345	
RT Neg. – RT Pos. Mis.*	10 ms	1.003	0.995–1.011	0.423	
Emotional Memory (EmMem)					
Previous episodes−10 years	*n*	*1.118*	*1.040–1.201*	*0.002*	
HDRS-score residual symptoms	*1 point*	*1.019*	*0.886–1.171*	*0.797*	*0.004*
Negative Acc. – Positive Acc.	n	0.923	0.748–1.138	0.453	
Negative Mis. – Positive Mis.	n	0.918	0.744–1.132	0.422	
Positive Acc. – Positive Mis.	n	0.924	0.763–1.120	0.422	
Negative Acc. – Negative Mis.	n	0.981	0.848–1.135	0.798	
(Negative Mis. – Positive Mis.)/(Positive Acc. – Negative Acc)§	%	0.934	0.755–1.155	0.528	
Facial Emotion Recognition (FERT)					
Previous episodes−10 years	*n*	*1.117*	*1.038–1.202*	*0.003*	
HDRS-score residual symptoms	*1 point*	*0.983*	*0.848–1.139*	*0.818*	
Angry Mis.	*n*	*1.038*	*1.006–1.070*	*0.019*	*0.001*
Sad Acc.	n	1.044	0.948–1.148	0.382	
Neutral Acc.	n	0.923	0.660–1.290	0.637	
Disgust Mis.	n	0.968	0.887–1.057	0.467	
Neutral Mis.	n	1.062	0.895–1.261	0.490	
Positive Acc. – Neutral Acc.	n	1.019	0.950–1.092	0.603	
Negative Acc. – Neutral Acc.	n	0.996	0.937–1.060	0.905	
Negative Mis. – Neutral Mis.	n	1.028	0.966–1.095	0.383	
Neutral Mis. – Positive Mis.	n	0.992	0.924–1.065	0.819	

*Outcome-specific composite scores were defined based on significant differences and interactions of outcomes between patients and controls (see **Table 2**). Variables in italics represent the final models, for which a p-value (χ^2) is given. All models contained previous episodes (last 10 years) and HDRS-score (residual symptoms). Selection of additional variables was done by forward stepwise selection from all listed outcome variables for each emotional bias task separately.*

**As not all subjects misclassified characteristics during emotional categorization, these mean reaction-times are based on less subjects (16 with recurrence and 16 resilient).*

§Cases with Positive Acc. – Negative Acc = 0 omitted from analyses (7 recurrent/7 resilient).

(82), who reported that 80% of patients with remitted MDD report self-blaming feelings as a significant symptom in their last episode. This might persist as residual symptom/bias contributing to a general vulnerability for recurrence, according to the revised learned helplessness model in which subjects blame themselves for failure in an overgeneralized way (83). The relevance of this misrecognition of neutral stimuli as negative, might be that a difficulty in accurately identifying subtle expression of emotion will hinder effective interpersonal interactions and/or social support in daily life (76). Since individuals use facial expressions to monitor emotional reactions to determine others' opinions and to adjust their behavior (76), important for social interactions, we propose that -in line with the general risk for depression of such impairments (84)- this impairment also plays an important role in recurrence. In fact, the observed association of recurrence with increased misclassifications as angry corroborates this idea. Moreover, the observed worse recognition of happy information/stimuli/faces when in a dysphoric mood (81) and the proposed difficulties in the processing of positive affect in MDD in general (76, 79–81) might additionally decrease resilience against (an impeding) recurrence. However, our facial recognition data suggest that the biases for positive material might be mood-congruent only, while difficulty in recognizing neutral expressions also exists without attempts to induce sad mood and are therefore "mood-incongruent" and might represent a trait (41).

Strengths and Limitations

An important strength of this study is our prospective design with 2.5 years follow-up and ADM-free patient sample. Moreover, cross-sectional studies comparing patients and controls usually do not control for a multitude of confounding factors such as mood state, anxiety disorder co-morbidity and trauma which make interpretations more difficult. Pharmacological interventions might alter neuropsychological and specifically emotional information processing, which can be observed already hours after intake (85–87). By excluding (remitted) patients using antidepressants, we avoid any influence of antidepressants on emotional bias, which was not possible in earlier studies [e.g., (40, 49, 86, 88)]. Although selection of unmedicated rrMDD-patients might represent a less severe

TABLE 6 | Performance of different Support Vector Machine algorithms predicting recurrence.

		Percentage of features selected		
		10%	50%	100%
Info in algorithm	**Total features**	**Accuracy (Sens/Spec)**	**Accuracy (Sens/Spec)**	**Accuracy (Sens/Spec)**
EmCat + EmMem	22	50.0 (54.3/44.8)	35.9 (48.6/20.7)	34.4 (34.3/34.5)
FERT	31	46.9 (42.9/51.7)	35.9 (34.3/37.9)	59.4 (65.7/51.7)
EmCat + EmMem + demographics	26	57.8 (60.0/55.2)	54.7 (57.1/51.7)	45.3 (40.0/51.7)
EmCat + EmMem + demographics (extended)	39	78.1 (68.6/89.7)* [2.8071; 0.002]	56.3 (54.3/58.6)	45.3 (31.4/62.1)
FERT + demographics	35	54.7 (45.7/65.5)	60.9 (62.9/58.6)	54.7 (57.1/51.7)
FERT + demographics (extended)	48	70.3 (60.0/82.8)* [1.8257; 0.034]	64.1 (68.6/58.6)	59.4 (60.0/58.6)
EmCat + EmMem + FERT	53	34.4 (28.6/41.4)	40.6 (45.7/34.5)	34.4 (34.3/34.5)
EmCat + EmMem + FERT + demographics	57	50.0 (40.0/62.1)	48.4 (51.4/44.8)	42.2 (45.7/37.9)
EmCat + EmMem + FERT + demographics (extended)	70	67.2 (57.1/79.3)	48.4 (60.0/34.5)	45.3 (42.9/48.3)
Demographics (extended) only	17	64.1 (51.4/79.3)	75.0 (71.4/79.3)* [2.4066; 0.008]	56.3 (54.3/58.6)

The SVM models were validated using a leave one out procedure (see methods). Data were used from all 64 participants for whom follow-up was available. Missing data points (e.g., for choices which were not made by a particular participant) were imputed as the mean of the training set. The C parameter was estimated over 50 values from 0.01 to 100 (the value used for prediction was the one which produced the highest accuracy in the training set). Demographics included gender, age, number of episodes in last 10 years and residual symptoms (HDRS-score), if indicated extended with CTQ-data.

*The classifiers marked with * performed significantly better than the a-priori recurrence-rate in the current sample (54.7%), between [] z-score and 1-tailed p-value are given. Positive and negative predictive values were not displayed as these are dependent on the recurrence-rate in the present sample.*

EmCat, Emotional Categorization Task; EmMem, Emotional Memory; FERT, Facial Emotion Recognition Task; Sens, Sensitivity; Spec, Specificity.

spectrum of the disease, the 55% recurrence rate rather contradicts this potential selection bias.

Nevertheless, some limitations must be addressed. First, as mentioned earlier, we did not apply a mood induction before measuring the cognitive biases reported in this manuscript. Previous research found that cognitive biases are present after recovery from a depressive episode but may remain dormant until activated by negative mood or stress (18). A mood-induction procedure may be required to reveal such biases. Although we deliberately performed the mood-induction procedure after these neurocognitive tasks (64), this might have obscured biases in tasks using self-relevant material (EmCAT, EmMem), as discussed. As euthymia does not exclude dysphoria or dysthymic affect, these fluctuations might have influenced the assessments, challenging their mood-incongruency. Nevertheless, we assessed severity of depression of all subjects when doing the tests and excluded patients who were depressed at the time of testing. Therefore, in absence of a mood-induction, we think we can interpret our results to represent more trait-like disturbances instead of sad mood congruent (i.e., state-dependent) phenomena. This might be relevant for daily life and clinical applicability where a mood-induction most often is unfeasible (89).

Second, emotional biases are more profound when stimuli are self-referent. The EmCAT must be considered partly self-referent (i.e., self-relevant), since we asked participants to indicate agreeableness of self-referent characteristics. It would be interesting to know whether the use of (verbal) self-referential material in e.g., a SRET or a memory task for autobiographical material would yield comparable differences between rrMDD-patients and controls and/or more associations with prospective recurrence. In addition, our assessment of emotional memory might be more sensitive by assessing retrieval in interaction with emotional load (90). Nevertheless, the validity of the tasks used and their sensitivity to detect biases has been shown previously, albeit primarily in depressed subjects (60, 61, 85).

Third, sex differences in emotion identification (e.g., in faces) have been identified in previous studies (81, 91, 92), therefore several studies included only women (49, 81). We included both sexes, which might have obscured our findings. *Post-hoc* analyses in the current study indeed revealed a gender*valence interaction for the accuracy of positive vs. neutral faces (FERT), but without a gender*valence*group interaction, which was our primary interest. However, for the significant accuracy*valence*group interaction for reaction times in the EmCAT we also found an interaction with gender (mixed model; accuracy*valence*group*gender interaction; [$F_{(5,3283.92)} = 18.81$; $p < 0.001$]). This indicated that male rrMDD-patients were both faster in response to positive (especially incorrect) and negative characteristics than male controls, while females rrMDD-patients were overall slower in response to both positive (especially incorrect) and negative characteristics (data available on request). This gender effect in the EmCAT needs further exploration in future studies.

Fourth, the number of observations of incorrect classifications of self-relevant characteristics in the EmCAT was low, which might therefore be a false-positive result, so this result should be considered preliminary. Also, the statistical power to observe associations with recurrence might have been too limited to

exclude the possibility of false negative findings. Moreover, we did not apply a multiple comparison correction, so our results must be regarded as exploratory. Ideally, selecting variables for prospective prediction on the basis of their abnormality compared with healthy controls would also requiring multiple testing correction. When we would e.g., apply a Bonferroni correction, known to be the most conservative, the association with recurrence will be non-significant, which merits cautious interpretation of this result. Moreover, although SVM algorithms are widely used and robust, the leave-one-out cross validation method has been criticized for overestimating accuracy of prediction and poor generalization.

Fifth, the vulnerability to have a recurrence mediated by emotional biases might only become relevant in interaction with daily stressors or maybe more importantly: daily hassles (93). As such, such stressors/daily hassles might better be modeled as time-dependent covariates in future analyses.

Finally, Hertel concluded that depressed individuals have the ability to perform at the level of healthy control participants in structured situations but have difficulty doing so when situations are unconstrained or when they are left to their own initiative (94). Although we abstained from an artificial mood-induction when examining biases, our tests were also acquired in a laboratory setting, which might have reduced their sensitivity or generalizability (76).

CONCLUSION

When investigating emotional biases in drug-free, remitted recurrently depressed patients, we observed biases toward emotionally negative stimuli and poorer recognition of neutral facial expressions. Overall, our data suggests a persisting (also mood-incongruent) emotional bias when patients with recurrent depression are in remission. Moreover, the number of misclassifications as angry-faces and the task-based composite score for the emotional memory were independently associated with the time to recurrence during 2.5 years of follow-up. We propose that these persisting biases might be mechanistically important for recurrence and prevention thereof.

AUTHOR CONTRIBUTIONS

HR, CH, and AS designed the study. HR, RM, and CF performed recruitment and data-acquisition of participants and daily management of the study. PS, RM, MB, and HR performed analyses and interpreted the data. HR drafted the manuscript with assistance of PS, RM, NI, AT, MB, and JV. All authors provided feedback on the initial versions of the manuscript and approved the final version.

FUNDING

The start of the DELTA-neuroimaging study was funded by the Dutch Brain Foundation [Hersenstichting; Grant #2009(2)-72]. Further support was obtained by unrestricted personal grants from the AMC to RM (AMC PhD Scholarship) and CF (AMC MD-PhD Scholarship). HR is supported by a NWO/ZonMW VENI-grant (#016.126.059).

ACKNOWLEDGMENTS

We thank the patients and controls for their participation in this study.

REFERENCES

1. Bockting CLH, Spinhoven P, Wouters LF, Koeter MWJ, Schene AH, DELTA study group. Long-term effects of preventive cognitive therapy in recurrent depression: a 5.5-year follow-up study. *J Clin Psychiatry.* (2009) 70:1621–8. doi: 10.4088/JCP.08m04784blu
2. Smith K. Mental health: a world of depression. *Nature.* (2014) 515:180–1. doi: 10.1038/515180a
3. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman ATF. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand.* (2009) 122:184–91. doi: 10.1111/j.1600-0447.2009.01519.x
4. Kessing LV, Hansen MG, Andersen PK, Angst J. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. *Acta Psychiatr Scand.* (2004) 109:339–44. doi: 10.1046/j.1600-0447.2003.00266.x
5. Prien RF, Carpenter LL, Kupfer DJ. The definition and operational criteria for treatment outcome of major depressive disorder. A review of the current research literature. *Arch Gen Psychiatry.* (1991) 48:796–800.
6. ten Doesschate MC, Bockting CLH, Koeter MWJ, Schene AH, DELTA study group. Prediction of recurrence in recurrent depression: a 5.5-year prospective study. *J Clin Psychiatry.* (2010) 71:984–91. doi: 10.4088/JCP.08m04858blu
7. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. *Annu Rev Clin Psychol.* (2005) 1:167–95. doi: 10.1146/annurev.clinpsy.1.102803.143916
8. Leyman L, De Raedt R, Schacht Ri, Koster EHW. Attentional biases for angry faces in unipolar depression. *Psychol Med.* (2007) 37:393. doi: 10.1017/S003329170600910X
9. Peckham AD, McHugh RK, Otto MW. A meta-analysis of the magnitude of biased attention in depression. *Depress Anxiety.* (2010) 27:1135–42. doi: 10.1002/da.20755
10. Johnson SL, Joormann J, Gotlib IH. Does processing of emotional stimuli predict symptomatic improvement and diagnostic recovery from major depression? *Emotion.* (2007) 7:201–6. doi: 10.1037/1528-3542.7.1.201
11. Frings C, Wentura D, Holtz M. Dysphorics cannot ignore unpleasant information. *Cogn Emot.* (2007) 21:1525–34. doi: 10.1080/02699930601054042
12. Joormann J. Attentional bias in dysphoria: the role of inhibitory processes. *Cogn Emot.* (2004) 18:125–47. doi: 10.1080/02699930244000480
13. Goeleven E, De Raedt R, Baert S, Koster EHW. Deficient inhibition of emotional information in depression. *J Affect Disord.* (2006) 93:149–57. doi: 10.1016/j.jad.2006.03.007
14. Atchley RA, Ilardi SS, Young KM, Stroupe NN, O'Hare AJ, Bistricky SL, et al. Depression reduces perceptual sensitivity for positive words and pictures. *Cogn Emot.* (2012) 26:1359–70. doi: 10.1080/02699931.2012.660134
15. Nandrino JL, Dodin V, Martin P, Henniaux M. Emotional information processing in first and recurrent major depressive episodes. *J Psychiatr Res.* (2004) 38:475–84. doi: 10.1016/j.jpsychires.2004.03.002
16. Zetsche U, Joormann J. Components of interference control predict depressive symptoms and rumination cross-sectionally and at six months follow-up. *J Behav Ther Exp Psychiatry.* (2011) 42:65–73. doi: 10.1016/j.jbtep.2010.06.001
17. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S. Rethinking rumination. *Perspect Psychol Sci.* (2008) 3:400–24. doi: 10.1111/j.1745-6924.2008.00088.x
18. Scher CD, Ingram RE, Segal ZV. Cognitive reactivity and vulnerability: empirical evaluation of construct activation and cognitive diatheses

in unipolar depression. *Clin Psychol Rev.* (2005) 25:487–510. doi: 10.1016/j.cpr.2005.01.005
19. Segal ZV, Kennedy S, Gemar M, Hood K, Pedersen R, Buis T. Cognitive reactivity to sad mood provocation and the prediction of depressive relapse. *Arch Gen Psychiatry.* (2006) 63:749. doi: 10.1001/archpsyc.63.7.749
20. Moulds ML, Kandris E, Williams AD, Lang T, Yap C, Hoffmeister K. An investigation of the relationship between cognitive reactivity and rumination. *Behav Ther.* (2008) 39:65–71. doi: 10.1016/j.beth.2007.05.001
21. Wichers M, Peeters F, Geschwind N, Jacobs N, Simons CJP, Derom C, et al. Unveiling patterns of affective responses in daily life may improve outcome prediction in depression: a momentary assessment study. *J Affect Disord.* (2010) 124:191–5. doi: 10.1016/j.jad.2009.11.010
22. Rive MM, van Rooijen G, Veltman DJ, .Phillips ML, Schene AH, Ruhé HG. Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neurosci Biobehav Rev.* (2013) 37:2529–53. doi: 10.1016/j.neubiorev.2013.07.018
23. Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. *Eur J Pharmacol.* (2010) 626:83–6. doi: 10.1016/j.ejphar.2009.08.046
24. De Raedt R, Koster EHW, Joormann J. Attentional control in depression: a translational affective neuroscience approach. *Cogn Affect Behav Neurosci.* (2010) 10:1–7. doi: 10.3758/CABN.10.1.1
25. Gohier B, Ferracci L, Surguladze SA, Lawrence E, El Hage W, Kefi MZ, et al. Cognitive inhibition and working memory in unipolar depression. *J Affect Disord.* (2009) 116:100–5. doi: 10.1016/j.jad.2008.10.028
26. Joormann J, Arditte KA. Cognitive aspects of depression. In: Gotlib IH, Hammen C, editors. *Handbook of Depression.* New York, NY: Guilford Press. p. 298–321.
27. De Raedt R, Koster EHW. Understanding vulnerability for depression from a cognitive neuroscience perspective: a reappraisal of attentional factors and a new conceptual framework. *Cogn Affect Behav Neurosci.* (2010) 10:50–70. doi: 10.3758/CABN.10.1.50
28. Leppänen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr Opin Psychiatry.* (2006) 19:34–9. doi: 10.1097/01.yco.0000191500.46411.00
29. Vanderhasselt MA, De Raedt R. Impairments in cognitive control persist during remission from depression and are related to the number of past episodes: an event related potentials study. *Biol Psychol.* (2009) 81:169–76. doi: 10.1016/j.biopsycho.2009.03.009
30. van Oostrom I, Franke B, Arias Vasquez A, Rinck M, Tendolkar I, Verhagen M, et al. Never-depressed females with a family history of depression demonstrate affective bias. *Psychiatry Res.* (2013) 205:54–8. doi: 10.1016/j.psychres.2012.08.004
31. Joormann J, Talbot L, Gotlib IH. Biased processing of emotional information in girls at risk for depression. *J Abnorm Psychol.* (2007) 116:135–43. doi: 10.1037/0021-843X.116.1.135
32. Taylor L, Ingram RE. Cognitive reactivity and depressotypic information processing in children of depressed mothers. *J Abnorm Psychol.* (1999) 108:202–10.
33. Vrijsen JN, van Oostrom I, Arias-Vásquez A, Franke B, Becker ES, Speckens A. Association between genes, stressful childhood events and processing bias in depression vulnerable individuals. *Genes Brain Behav.* (2014) 13:508–16. doi: 10.1111/gbb.12129
34. Vrijsen JN, Tendolkar I, Arias-Vásquez A, Franke B, Schene AH, Fernández G, et al. Interaction of the 5-HTTLPR and childhood trauma influences memory bias in healthy individuals. *J Affect Disord.* (2015) 186:83–9. doi: 10.1016/j.jad.2015.06.008
35. Chan SWY, Goodwin GM, Harmer CJ. Highly neurotic never-depressed students have negative biases in information processing. *Psychol Med.* (2007) 37:1281–91. doi: 10.1017/S0033291707000669
36. Servaas MN, Riese H, Renken RJ, Wichers M, Bastiaansen JA, Figueroa CA, et al. Associations between daily affective instability and connectomics in functional subnetworks in remitted patients with recurrent major depressive disorder. *Neuropsychopharmacology.* (2017) 42:2583–92. doi: 10.1038/npp.2017.65
37. MacLeod C, Rutherford E, Campbell L, Ebsworthy G, Holker L. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. *J Abnorm Psychol.* (2002) 111:107–23. doi: 10.1037/0021-843X.111.1.107
38. Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG. Cognitive impairment in the euthymic phase of chronic unipolar depression. *J Nerv Ment Dis.* (1997) 185:748–54.
39. Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. *Br J Psychiatry.* (2001) 178:200–6. doi: 10.1192/bjp.178.3.200
40. Maalouf FT, Clark L, Tavitian L, Sahakian BJ, Brent D, Phillips ML. Bias to negative emotions: a depression state-dependent marker in adolescent major depressive disorder. *Psychiatry Res.* (2012) 198:28–33. doi: 10.1016/j.psychres.2012.01.030
41. Leppänen JM, Milders M, Bell JS, Terriere E, Hietanen JK. Depression biases the recognition of emotionally neutral faces. *Psychiatry Res.* (2004) 128:123–33. doi: 10.1016/j.psychres.2004.05.020
42. Zvielli A, Vrijsen JN, Koster EHW, Bernstein A. Attentional bias temporal dynamics in remitted depression. *J Abnorm Psychol.* (2016) 125:768–76. doi: 10.1037/abn0000190
43. Sears CR, Newman KR, Ference JD, Thomas CL. Attention to emotional images in previously depressed individuals: an eye-tracking study. *Cognit Ther Res.* (2011) 35:517–28. doi: 10.1007/s10608-011-9396-5
44. Farb NAS, Irving JA, Anderson AK, Segal ZV. A two-factor model of relapse/recurrence vulnerability in unipolar depression. *J Abnorm Psychol.* (2015) 124:38–53. doi: 10.1037/abn0000031
45. Joormann J, Gotlib IH. Selective attention to emotional faces following recovery from depression. *J Abnorm Psychol.* (2007) 116:80–5. doi: 10.1037/0021-843X.116.1.80
46. Everaert J, Podina IR, Koster EHW. A comprehensive meta-analysis of interpretation biases in depression. *Clin Psychol Rev.* (2017) 58:33–48. doi: 10.1016/j.cpr.2017.09.005
47. Gethin JA, Lythe KE, Workman CI, Mayes A, Moll J, Zahn R. Early life stress explains reduced positive memory biases in remitted depression. *Eur Psychiatry.* (2017) 45:59–64. doi: 10.1016/j.eurpsy.2017.06.011
48. Vrijsen JN, Becker ES, Arias-Vásquez A, van Dijk MK, Speckens A, Oostrom I. What is the contribution of different cognitive biases and stressful childhood events to the presence and number of previous depressive episodes? *Psychiatry Res.* (2014) 217:134–42. doi: 10.1016/j.psychres.2014.02.033
49. LeMoult J, Kircanski K, Prasad G, Gotlib IH. Negative self-referential processing predicts the recurrence of major depressive episodes. *Clin Psychol Sci.* (2017) 5:174–81. doi: 10.1177/2167702616654898
50. Gotlib IH, Joormann J. Cognition and depression: current status and future directions. *Annu Rev Clin Psychol.* (2010) 6:285–312. doi: 10.1146/annurev.clinpsy.121208.131305
51. Mathews A, MacLeod C. Cognitive approaches to emotion and emotional disorders. *Annu Rev Psychol.* (1994) 45:25–50. doi: 10.1146/annurev.ps.45.020194.000325
52. Browning M, Holmes EA, Charles M, Cowen PJ, Harmer CJ. Using attentional bias modification as a cognitive vaccine against depression. *Biol Psychiatry.* (2012) 72:572–9. doi: 10.1016/j.biopsych.2012.04.014
53. Cristea IA, Kok RN, Cuijpers P. Efficacy of cognitive bias modification interventions in anxiety and depression: Meta-analysis. *Br J Psychiatry.* (2015) 206:7–16. doi: 10.1192/bjp.bp.114.146761
54. Jones EB, Sharpe L. Cognitive bias modification: A review of meta-analyses. *J Affect Disord.* (2017) 223:175–83. doi: 10.1016/j.jad.2017.07.034
55. Vrijsen JN, Fischer VS, Müller BW, Scherbaum N, Becker ES, Rinck M, et al. Cognitive bias modification as an add-on treatment in clinical depression: Results from a placebo-controlled, single-blinded randomized control trial. *J Affect Disord.* (2018) 238:342–50. doi: 10.1016/j.jad.2018.06.025
56. Hakamata Y, Lissek S, Bar-Haim Y, Britton JC, Fox NA, Leibenluft E, et al. Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. *Biol Psychiatry.* (2010) 68:982–90. doi: 10.1016/j.biopsych.2010.07.021
57. Hertel PT, Mathews A. Cognitive Bias modification past perspectives, current findings, and future applications. *Perspect Psychol Sci.* (2011) 6:521–36. doi: 10.1177/1745691611421205
58. Koster EH, Hoorelbeke K. Cognitive bias modification for depression. *Curr Opin Psychol.* (2015) 4:119–23. doi: 10.1016/j.copsyc.2014.11.012

59. Kruijt AW, Putman P, Van der Does W. A multiple case series analysis of six variants of attentional bias modification for depression. *ISRN Psychiatry.* (2013) 2013:414170. doi: 10.1155/2013/414170
60. Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. *Br J Psychiatry.* (2009) 195:102–8. doi: 10.1192/bjp.bp.108.051193
61. Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. *Am J Psychiatry.* (2009) 166:1178–84. doi: 10.1176/appi.ajp.2009.09020149
62. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* (1967) 6:278–96.
63. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition (SCID-I/P version 2.0)*. Translated in Dutch. In: Groenestijn MAC, Akkerhuis GW, Kupka RW, Schneider N, Nolen LisseWA, editors. Swets & Zeitlinger B.V. (1999).
64. Mocking RJT, Figueroa CA, Rive MM, Geugies H, Servaas MN, Assies J, et al. Vulnerability for new episodes in recurrent major depressive disorder: protocol for the longitudinal delta-neuroimaging cohort study. *BMJ Open.* (2016) 6:e009510. doi: 10.1136/bmjopen-2015-009510
65. Schmand B, Bakker D, Saan R, Louman J. [The Dutch reading test for adults: a measure of premorbid intelligence level]. *Tijdschr Gerontol Geriatr.* (1991) 22:15–9.
66. Mocking RJT, Patrick Pflanz C, Pringle A, Parsons E, McTavish SF, Cowen PJ, et al. Effects of short-term varenicline administration on emotional and cognitive processing in healthy, non-smoking adults: a randomized, double-blind, study. *Neuropsychopharmacology.* (2013) 38:476–84. doi: 10.1038/npp.2012.205
67. Hammen C, Zupan BA. Self-schemas, depression, and the processing of personal information in children. *J Exp Child Psychol.* (1984) 37:598–608.
68. Derry PA, Kuiper NA. Schematic processing and self-reference in clinical depression. *J Abnorm Psychol.* (1981) 90:286–97.
69. Ekman P, Friesen WV. *Pictures of Facial Affect Brochure.* San Francisco, CA: Consulting Psychologists Press (1976).
70. Browning M, Kingslake J, Dourish CT, Goodwin GM, Harmer CJ, Dawson GR. Predicting treatment response to antidepressant medication using early changes in emotional processing. *Eur Neuropsychopharmacol.* (2018) 29:66–75. doi: 10.1016/j.euroneuro.2018.11.1102
71. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry.* (1994) 151:1132–6.
72. Scher CD, Stein MB, Asmundson GJG, Mccreary DR, Forde DR. The childhood trauma questionnaire in a community sample: psychometric properties and normative data. *J Trauma Stress.* (2001) 14:843–57. doi: 10.1023/A:1013058625719
73. Hastie T, Friedman J, Tibshirani R. Model assessment and selection. In: Hastie T, Friedman J, Tibshirani R, editors. *The Elements of Statistical Learning.* New York, NY: Spinger-Verlag (2009). p. 193–224.
74. Huang YM, Du SX. Weighted support vector machine for classification with uneven training class sizes. In: *Proceedings of the 2005 International Conference on Machine Learning and Cybernetics*. Guangzhou.
75. Verhage F, Werff, Van der JJ. [An analysis of variance based on the Groninger intelligence scores]. *Ned Tijdschr Psychol.* (1964) 19:497–509.
76. LeMoult J, Gotlib IH. Depression: a cognitive perspective. *Clin Psychol Rev.* (2018). doi: 10.1016/j.cpr.2018.06.008. [Epub ahead of print].
77. Fritzsche A, Dahme B, Gotlib IH, Joormann J, Magnussen H, Watz H, et al. Specificity of cognitive biases in patients with current depression and remitted depression and in patients with asthma. *Psychol Med.* (2010) 40:815–26. doi: 10.1017/S0033291709990948
78. Figueroa CA, Mocking RJT, van Wingen G, Martens S, Ruhé HG, Schene AH. Aberrant default-mode network-hippocampus connectivity after sad memory-recall in remitted-depression. *Soc Cogn Affect Neurosci.* (2017) 12:1803–13. doi: 10.1093/scan/nsx108
79. Joormann J, Gotlib IH. Is this happiness I see? Biases in the identification of emotional facial expressions in depression and social phobia. *J Abnorm Psychol.* (2006) 115:705–14. doi: 10.1037/0021-843X.115.4.705
80. Surguladze SA, Young AW, Senior C, Brébion G, Travis MJ, Phillips ML. Recognition accuracy and response bias to happy and sad facial expressions in patients with major depression. *Neuropsychology.* (2004) 18:212–8. doi: 10.1037/0894-4105.18.2.212
81. LeMoult J, Joormann J, Sherdell L, Wright Y, Gotlib IH. Identification of emotional facial expressions following recovery from depression. *J Abnorm Psychol.* (2009) 118:828–33. doi: 10.1037/a0016944
82. Zahn R, Lythe KE, Gethin JA, Green S, Deakin JFW, Young AH, et al.The role of self-blame and worthlessness in the psychopathology of major depressive disorder. *J Affect Disord.* (2015) 186:337–41. doi: 10.1016/j.jad.2015.08.001
83. Abramson LY, Seligman ME, Teasdale JD. Learned helplessness in humans: critique and reformulation. *J Abnorm Psychol.* (1978) 87:49–74. doi: 10.1037/0021-843X.87.1.49
84. Joiner TE, Timmons KA. Depression in its interpersonal context. In: Gotlib I, Hammen CL, editors. *Handbook of Depression*. New York, NY: Guilford Press. p. 322–39.
85. Harmer CJ. Antidepressant drug action: a neuropsychological perspective. *Depress Anxiety.* (2010) 27:231–3. doi: 10.1002/da.20680
86. Delaveau P, Jabourian M, Lemogne C, Guionnet S, Bergouignan L, Fossati P. Brain effects of antidepressants in major depression: A meta-analysis of emotional processing studies. *J Affect Disord.* (2011) 130:66–74. doi: 10.1016/j.jad.2010.09.032
87. Pringle A, Browning M, Cowen PJ, Harmer CJ. A cognitive neuropsychological model of antidepressant drug action. *Prog Neuro-Psychopharmacology Biol Psychiatry.* (2011) 35:1586–92. doi: 10.1016/j.pnpbp.2010.07.022
88. Chambers R, Lo BCY, Allen NB. The impact of intensive mindfulness training on attentional control, cognitive style, and affect. *Cogn Ther Res.* (2008) 32:303–22. doi: 10.1007/s10608-007-9119-0
89. Figueroa CA, Mocking RJT, Mahmoud GA, Koeter MW, Bockting CL, van der Does W, et al. The measurement of cognitive reactivity to sad mood in patients remitted from major depressive disorder. *Br J Clin Psychol.* (2018) 57:313–27. doi: 10.1111/bjc.12175
90. Dobson KS, Shaw BF. Specificity and stability of self-referent encoding in clinical depression. *J Abnorm Psychol.* (1987) 96:34–40.
91. Bouhuys AL, Geerts E, Gordijn MC. Gender-specific mechanisms associated with outcome of depression: perception of emotions, coping and interpersonal functioning. *Psychiatry Res.* (1999) 85:247–61.
92. Li H, Yuan J, Lin C. The neural mechanism underlying the female advantage in identifying negative emotions: an event-related potential study. *Neuroimage.* (2008) 40:1921–9. doi: 10.1016/j.neuroimage.2008.01.033
93. Bockting CL, Spinhoven P, Koeter MW, Wouters LF, Visser I, Schene AH. Differential predictors of response to preventive cognitive therapy in recurrent depression: a 2-year prospective study. *PsychotherPsychosom.* (2006) 75:229–36. doi: 10.1159/000092893
94. Hertel PT. Memory for emotional and nonemotional events in depression: a question of habit? In: Reisberg D, Hertel PT, editors. *Memory and Emotion*. New York, NY: Oxford University Press. p. 186–216.

Conflict of Interest Statement: MB has received travel expenses from Lundbeck for attending conferences, and acted as a consultant for Johnson and Johnson. He is employed part time by P1vital Ltd and owns shares in P1vital Products Ltd. CH has served as a paid consultant or speaker for Lundbeck, Servier, P1vital, and Pfizer. She has received grant income from Johnson and Johnson, UCB, and P1vital.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 23 September 2019
doi: 10.3389/fpsyt.2019.00639

Postdecision Evidence Integration and Depressive Symptoms

Madeleine E. Moses-Payne[1†], Max Rollwage[2,3†], Stephen M. Fleming[2,3‡] and Jonathan P. Roiser[1‡]*

[1] Institute of Cognitive Neuroscience, University College London, London, United Kingdom, [2] Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom, [3] Department for Imaging Neurosciences, Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London, United Kingdom

OPEN ACCESS

Edited by:
Catherine Harmer, Warneford Hospital, United Kingdom

Reviewed by:
Rebecca Strawbridge, King's College London, United Kingdom
Liliana Capitao, University of Oxford, United Kingdom
Alexander Kaltenboeck, University of Oxford, United Kingdom

****Correspondence:***
Madeleine E. Moses-Payne
m.payne@ucl.ac.uk

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work and share senior authorship

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *19 February 2019*
Accepted: *07 August 2019*
Published: *23 September 2019*

Citation:
Moses-Payne ME, Rollwage M, Fleming SM and Roiser JP (2019) Postdecision Evidence Integration and Depressive Symptoms. Front. Psychiatry 10:639. doi: 10.3389/fpsyt.2019.00639

Background: Metacognition, or the ability to reflect on one's own thoughts, may be important in the development of depressive symptoms. Recent work has reported that depressive symptoms were associated with lower metacognitive bias (overall confidence) during perceptual decision making and a trend toward a positive association with metacognitive sensitivity (the ability to discriminate correct and incorrect decisions). Here, we extended this work, investigating whether confidence judgments are more malleable in individuals experiencing depressive symptoms. We hypothesized that depressive symptoms would be associated with greater adjustment of confidence in light of new evidence presented after a perceptual decision had been made.

Methods: Participants (N = 416) were recruited *via* Amazon Mechanical Turk. Metacognitive confidence was assessed through two perceptual decision-making tasks. In both tasks, participants made a decision about which of two squares contained more dots. In the first task, participants rated their confidence immediately following the decision, whereas in the second task, participants observed new evidence (always in the same direction as initial evidence) before rating their confidence. Participants also completed questionnaires measuring depressive symptoms and self-esteem.

Analysis: Metacognitive bias was calculated as overall mean confidence, whereas metacognitive sensitivity was calculated using meta-d' (a response-bias free measure of how closely confidence tracks task performance) in the first task. Postdecision evidence integration (PDEI) was defined as the change in confidence following postdecision evidence on the second task.

Results: Participants with more depressive symptoms made greater confidence adjustments (i.e., greater PDEI) in light of new evidence ($\beta = 0.119$, $p = 0.045$), confirming our main hypothesis. We also observed that lower overall confidence was associated with greater depressive symptoms, although this narrowly missed statistical significance ($\beta = -0.099$, $p = 0.056$), and we did not find an association between metacognitive sensitivity (meta-d') and depressive symptoms. Notably, self-esteem was robustly associated with overall confidence ($\beta = 0.203$, $p < 0.001$), which remained significant when controlling for depressive symptoms.

Conclusions: We found that individuals with depressive symptoms were more influenced by postdecisional evidence, adjusting their confidence more in light of new evidence.

Individuals with low self-esteem were less confident about their initial decisions. This study should be replicated in a clinically depressed sample.

Keywords: metacognition, depression, self-esteem, decision making, confidence, postdecision evidence

BACKGROUND

Individuals have the ability to reflect on and report their mental states. In this way, decisions are usually accompanied by a degree of confidence (or uncertainty) regarding accuracy, which is often termed a metacognitive judgment (1). The ability to accurately track performance with confidence ratings is known as metacognitive ability (2), and this varies substantially among individuals (3).

Early Investigations Into Metacognition and Depression

The ability to reflect on our thoughts may be important in the development, maintenance of, and recovery from a depressive episode. Early investigations into metacognition in depression focused on self-reinforcement (4, 5). In these studies, participants were asked to evaluate their performance by retrospectively administering self-reward (or self-punishment) by choosing the number of tokens (that translated into monetary reward) they believed they deserved for their performance on various tasks. Depressed patients were consistently less willing to reward, and more willing to punish, themselves (4, 5). However, because self-evaluation in these studies entailed explicit reinforcement, this pattern of results is difficult to interpret. An alternative explanation is that depressed patients in fact believed that they performed as well as nondepressed individuals, but that they did not deserve reward (or deserved punishment) despite good performance. This would align with the well-known tendency for depressed patients to experience excessive feelings of guilt, leading to the belief that they deserve punishment (6, 7).

Confidence Judgments in Depression

In the late 1970s, the idea of depressive realism was proposed (8), which stimulated further investigation into metacognition in depression. Alloy and Abramson (8) suggested that depressed patients are sadder but wiser, that is, that they hold a more realistic view of themselves and the world compared with healthy individuals who are influenced by a rose-tinted positive bias. This challenged both clinical convention and earlier cognitive models of depression [e.g., Refs. (9, 10)], which focused on the idea that thoughts in depressed patients were dominated by negative schemata perpetuated through negative biases in the processing of new information. By contrast, according to the depressive realism account, healthy participants should show a positive bias, rating their performance more favorably (overconfidence), whereas depressed individuals should report a more accurate account of their performance.

The evidence for the depressive realism hypothesis is mixed, especially when assessed *via* confidence in decision-making paradigms. In these experiments, a metric of calibration is inferred by comparing reported percentage correct (confidence) to actual percentage correct (accuracy). When confidence is rated after the decision task, depressed patients have commonly been found to exhibit pessimistic calibration, being approximately twice as likely to rate their performance below chance compared to healthy controls (11–14). However, such posttest differences in metacognitive bias could be influenced by a negative memory bias. In other designs, confidence ratings are made on a trial-by-trial basis. Depressed participants seem to show a lowered overconfidence effect on such tasks, meaning that their judgments more accurately reflect their long-run performance (11, 15, 16), which would be consistent with depressive realism. However, in some studies, this difference was specific to correct trials only (14, 17) or depended on whether the participant expected to do badly before the test (11), indicating that depressive realism may be context-dependent.

Quiles et al. (18) measured metacognitive awareness (as termed by the authors) using a more sophisticated method—by calculating Hamann's coefficient (19). This involves creating a contingency table of concordance and disconcordance between performance and confidence scores. Hamann's coefficient was then used as a measure of metacognitive awareness on four different cognitive tasks. This study detected a positive relationship between metacognitive awareness and depression scores on a facial emotion recognition task (i.e., confidence ratings were more closely aligned with actual performance in depressed individuals). However, there was no evidence of such an association with metacognitive awareness on tests of executive function, digit span, or episodic memory. Quiles et al. (18) also measured self-esteem using Rosenberg's Self-Esteem Questionnaire (20) but found no association with metacognitive awareness.

One difficulty in interpreting the above findings is that these measures conflate metacognitive bias (the extent to which subjects have the tendency to rate high or low confidence) with metacognitive sensitivity (the ability to discriminate correct from incorrect decisions). However, in theory, the overall level of confidence (metacognitive bias) is independent of the ability to discriminate between correct and incorrect decisions (metacognitive sensitivity) as one can have overall relatively low confidence but still appropriately differentiate between correct and incorrect decisions (i.e., selectively assigning higher confidence to correct decisions). Such concerns have led to novel computational methods to assess metacognitive sensitivity, which helps formalize different facets of metacognition and create more precise evaluations of the bias and sensitivity of metacognitive judgments (2). This dissociation between confidence bias and metacognitive sensitivity has important theoretical implications regarding

the association with depression because these two concepts may track different psychological phenomena, that is, general negative self-evaluation versus depressive realism.

Association Between Metacognitive Sensitivity and Depression

In an effort to tease apart these constructs, Rouault et al. (21) recently utilized computational methods and trial-by-trial confidence ratings to separately measure confidence bias and metacognitive sensitivity, alongside questionnaires assessing various symptoms of mental illness in two large online samples (N = 498 and N = 497). Using factor analysis to cluster symptoms, they found that high scores on questions loading onto a depression/anxiety factor were associated with significantly lower overall confidence in decision making. They also reported a trend-level association with metacognitive efficiency (the level of metacognitive sensitivity expected for a given level of task performance), such that participants with higher depression/anxiety factor scores were better able to discriminate between correct and incorrect trials.

Importantly, Rouault et al. (21) matched performance across all participants using a staircase procedure, meaning that differences in metacognitive judgments could not be explained by poorer performance in participants with high depression/anxiety factor scores. Equating task difficulty is crucial because unless groups are matched for accuracy, it is hard to dissociate metacognitive judgments from performance (because worse performance would be expected to elicit both lower overall confidence and impair trial-by-trial sensitivity) (21).

Postdecision Evidence Integration and Depressive Symptoms

Metacognitive evaluations have been tightly linked to postdecision evidence processing (22, 23) or the utilization of information not yet available for the decision itself (24). This process of ongoing evidence integration that occurs postdecision is especially important for recognising errors or changing one's mind (25–27). Thus, recent studies have sought to identify mechanisms supporting postdecision processing (28, 29) and link such mechanisms to metacognitive ability (30, 31). Investigating confidence adjustments based on postdecision evidence represents a natural extension of studies of metacognitive ability.

This might be especially important for our understanding of symptoms of depression, such as indecisiveness (more frequent changes of mind). Indecisiveness is a core symptom of depression, which may be important when considered alongside other interest-activity symptoms as a predictor of antidepressant treatment outcome (32). Previous research has found that dogmatism, which could be considered a rigid decisiveness, is associated with fewer changes of mind (31). Therefore, in the present study, we directly assessed the influence of postdecision evidence on confidence judgments and their relationship to symptoms of depression.

Role of Self-Esteem in Depression and Metacognition

Low self-esteem or self-worth are common symptoms of depression and play a central role in the classic cognitive models of depression (33). Low self-esteem can also prospectively predict depressive symptoms across the life span (34, 35).

Previous research has investigated the relationship between metacognition and self-efficacy, which is often considered a facet of self-esteem and describes a person's core beliefs about their ability to produce desired effects in their environment (36). Metacognition and self-efficacy may interact to guide learning. For example, a student's metacognitive judgment that they have better knowledge of one topic than another in an upcoming exam may lead them to study the latter more intensively. On the other hand, the same student's self-efficacy judgment about their ability to pass the exam may encourage (if optimistic) or hinder (if pessimistic) their motivation to study the less well-known topic. Such interactions between metacognition and self-esteem have been studied in relation to academic performance (37–39). However, to our knowledge, no previous study has examined the relationship between self-esteem and metacognitive function using cognitive tasks, which was one of the aims of the current study.

Current Study

In this study, we aimed to extend Rouault et al.'s (21) findings in a new sample of participants using a similar perceptual decision-making paradigm but also including a task that manipulated postdecision evidence. Alongside these two tasks, we measured depressive symptoms and self-esteem. As in Rouault et al. (21), participants were matched for perceptual discrimination performance using a staircase procedure. Therefore, we were able to discriminate between metacognitive bias (the overall degree of confidence), metacognitive sensitivity (the alignment between confidence ratings and accuracy), and postdecision evidence integration [(PDEI) the adjustment of confidence according to information provided after the decision was made].

First, we hypothesized that depressive symptoms would be associated with a lower metacognitive bias (i.e., lower overall confidence in decisions), as reported by Rouault et al. (21). Second, we hypothesized that depressive symptoms would be associated with higher metacognitive sensitivity (better calibration of confidence to accuracy, e.g., higher meta-d'), which did not survive correction for multiple comparisons in Rouault et al. (21). Finally, we hypothesized that depressive symptoms would be associated with a greater sensitivity to postdecision evidence, reflected in a greater increase in confidence following confirmatory evidence (indicating that the participant was correct) and a greater decrease in confidence following disconfirmatory evidence (indicating that the participant wasincorrect). This final variable was our primary outcome of interest and is novel to this experiment. We additionally included a measure of self-esteem to assess whether individual differences in metacognition were associated with this construct, which is highly relevant to depression. (34).

METHODS

Online Recruitment and Participants

Participants were recruited *via* Amazon Mechanical Turk. Subjects gave informed consent, and the study was approved by the Research Ethics Committee of University College London (study number 1260-003). Participants were paid a basic payment of $4.50 and earned a bonus of up to $3.50 (M = $3.01, SD = $0.22) based on task performance (explained below).

A total of 575 participants took part in the study, and 416 participants' data were analyzed. Data were collected as part of another project investigating the relationship between PDEI and radical political beliefs, which is reported elsewhere (31). The sample size was based on power calculations conducted in relation to the original politics effects reported in Rollwage et al. (31) because this was the main aim of the study. With N = 416, we had 80% power to detect an effect size (r) of 0.14 between depressive symptoms and metacognitive variables at p = 0.05 (two-tailed).

Out of 416 subjects, 219 were female and 196 were male (one participant selected "rather not say"). The mean age of the participants was 35.85 (range: 18–71 years). Participants reported a range of education levels, from high school to doctoral degree, with most participants having completed college-level education.

Participants had to be 18 years or older and were restricted to the United States and prevented from participating multiple times. Participants were excluded on the following grounds: if they failed to answer at least one of two catch questions presented within the questionnaires (n = 17); their perceptual discrimination performance exceeded 85% or dropped below 60% correct (indicating that the staircase procedure did not converge undermining the validity of the task, n = 90); they chose the same confidence rating more than 90% of the time (indicating that participants may not have engaged with the confidence reports, n = 11); their median confidence rating response time was below 850 ms (indicating a very quick and possibly careless rating, n = 19); they missed over 5% of trials (n = 21); or they missed questions in the depression questionnaire (n = 1). These data were collected as a follow-up to a previous experiment [as explained in Ref. (29)]; thus, these task-based exclusion criteria were defined *a priori* [based on Study 1 in Ref. (31)].

Overview of Procedure

Participants were given general information and instructions and completed an online consent form. Then, participants completed the calibration phase, which lasted about 10 min. Next, participants completed the confidence task (~10 min) followed by the PDEI task (~20–30 min) Please see **Figure 1** for task procedure. Finally, participants completed multiple questionnaires, including the Zung (40) depression questionnaire and the self-esteem rating [results relating to the other questionnaires are reported in Ref. (31)]. In total, participants spent about 60 min completing the experiment.

Experimental Design

Stimuli

Both tasks were programmed in JavaScript and were presented *via* the online platform Gorilla (https://gorilla.sc/). Stimuli for the perceptual decision consisted of two black squares (each 250*250 pixels) presented halfway up the screen, one to the right and one to the left of center. The squares were subdivided into 625 cells, which were randomly selected to be filled with dots. On each trial, one square always contained 313 cells filled with dots, and the other square contained a greater number of cells filled with dots—the exact difference in dot numbers was calibrated to individual participants and determined using a staircase procedure (described below). The configuration of dots (which cells contained/did not contain dots) was created randomly and changed four times during a single trial, with each configuration being presented for 150 ms. This gave the impression of flickering dots. The smaller the difference in dots between the two squares, the more difficult the perceptual decision. Within each trial, the square which contained more dots (left/right) remained constant.

Calibration

Performance was matched across participants using a staircase procedure, in which participants judged which of two squares contained more dots, but confidence ratings were not required. This procedure was used to identify the evidence strength (i.e., difference in dots) required to elicit approximately 71% accuracy for each participant. To do this, we used a 2-down–1-up staircase procedure that operates on the logarithm of the difference in the number of dots. Unlike either of the main tasks, during the calibration, participants were not asked for confidence ratings but were given visual feedback for each trial—showing a green frame around the chosen option if they were correct or a red frame around the chosen option if they were incorrect.

The calibration stage consisted of 120 trials. Participants completed 70 trials during the staircase procedure, and the average evidence strength of the last 25 trials was used for the initial decisions throughout the rest of the experiment. A further 50 trials were completed to be used to establish the dot difference for the high postdecision evidence strength trials. In these trials, the logarithm of the difference in the number of dots was multiplied by a factor of 1.3. These trials were interleaved within the other trials but only appeared after 20 "burn-in" trials (to allow the staircase to converge) and were yoked to the concurrent staircase value. This higher evidence strength evoked mean performance levels of 81.45% correct (SD = 10.43%).

Confidence Task (Task 1)

The confidence task consisted of 60 trials in total. In each trial, participants were again asked to make a judgment as to which square contained the larger number of dots. After making their decision, participants rated their confidence in their judgment by indicating the probability that their decision was correct. This was done by mouse click on a 9-point sliding scale, with the

lowest category labeled 0%, the highest category labeled 100%, and the midpoint labeled 50%.

Participants were incentivized to give accurate confidence ratings through a points system using a quadratic scoring rule (41):

$$\text{points} = 100 * [1 - (correct_i - conf_i)^2]$$

where $correct_i$ is 1 when the participant is correct on trial i and 0 when they are incorrect, and $conf_i$ is the participant's confidence rating on trial i. This means that to gain maximum points, participants should accurately report their confidence—the most points are earned when one is both maximally confident and correct or minimally confident and incorrect. For every 5,000 points earned, subjects received an extra $1.

Postdecision Evidence Integration Task (Task 2)

The PDEI task consisted of 120 trials, 60 with low postdecision evidence strength and 60 with high postdecision evidence strength. As in the confidence task, participants made a judgment as to which square contained more dots. After making this decision, participants were shown an additional sample of flickering dots. In half of the trials, the new sample was of the same strength to the initial sample (low postdecision evidence strength), and in the other half, the evidence was stronger (calibrated at 80% accuracy—high postdecision evidence strength). Participants rated their confidence in their initial decision only after seeing both predecision and postdecision samples. Importantly, the postdecision evidence was always in the same (correct) direction as the predecision evidence. Participants were instructed that the extra evidence was bonus information that could be used to inform their confidence ratings.

Depression Questionnaire and Self-Esteem Measure

Depressive symptoms were measured using Zung's (40) self-rating depression scale. This consists of 20 questions (10 positively worded and 10 negatively worded) assessing common symptoms of depression: mood disturbance (low mood, weeping), anhedonia (loss of interest or pleasure), physiological changes (trouble sleeping, constipation, weight

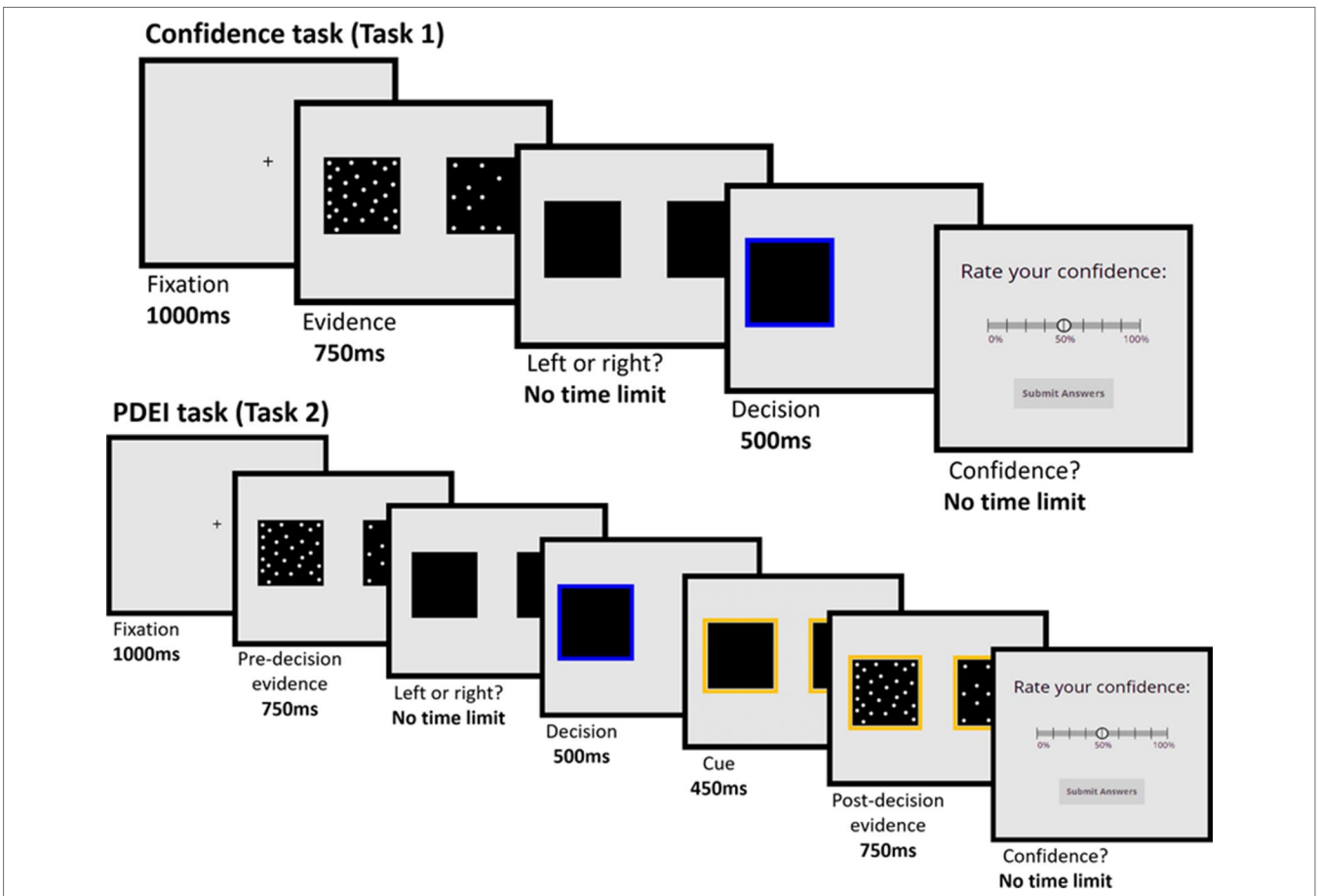

FIGURE 1 | Confidence task (Task 1) and Postdecision Evidence Integration (PDEI) task (Task 2). Participants were asked to judge which of two squares contained more flickering dots. In the Confidence task, participants immediately rated their confidence following their decision. In the PDEI task, participants viewed a new set of dots (always in the same direction as the predecision evidence. Half of trials showed evidence of the same strength as in predecision phase, whereas half of the trials showed evidence of greater strength) before rating their confidence in their original decision.

loss), psychomotor changes (restlessness, tiredness), and anxiety (heart rate, irritability).

Participants rate each statement on a 4-point scale, indicating whether the symptom had been experienced "a little of the time", "some of the time", "a good part of the time", or "most of the time" during the "past several days". Scores range from 20 to 80, with 20–49 considered "normal range", 50–59 "mildly depressed", 60–69 "moderately depressed", and 70 and above "severely depressed" (40).

We measured self-esteem using an adapted single-item self-rated question, which has been validated against Rosenberg's (20) 10-item scale (42). Participants were asked "How would you describe your overall self-esteem?" using a sliding scale from 0 "very low" to 100 "very high".

Analyses

All analyses used linear regression models. In all regression analyses, we employed robust fits (to reduce the influence of outliers), and all effects were tested two-tailed. This was conducted using MATLAB [Version R2017b, linear regression model (robust fit)], which uses a bisquare weighting function. All variables were standardized where possible (except for categorical variables, e.g., gender, education level, depression group).

Regression model 1 – dependent variable: depression score; predictor variables: demographic variables (age, gender, education level), performance variables (d', objective evidence strength, performance at higher postdecision evidence strength), and metacognitive variables (meta-d', overall confidence, PDEI) (**Figure 2**).

Regression model 2 – dependent variable: overall confidence; predictor variables: group (depressed/nondepressed), age, gender, performance (d'), and PDEI.

Regression model 3 – dependent variable: PDEI; predictor variables: group (depressed/nondepressed), age, gender, performance (d'), and overall confidence.

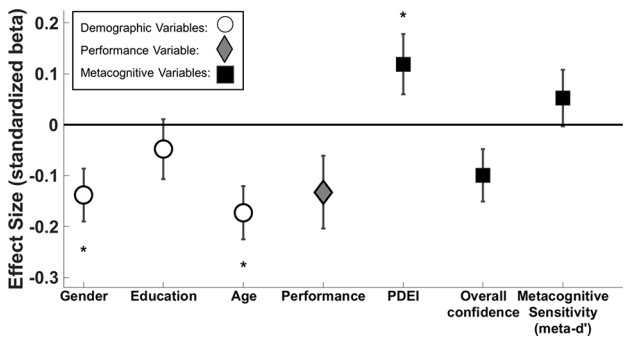

FIGURE 2 | Standardized beta coefficients (± standard error) of predictors of depression score. White circle markers indicate demographic variables, the gray diamond indicates perceptual performance (d' across both tasks), and black squares indicate metacognitive variables. We demonstrate significant effects of gender (β = -0.138, p = 0.008), age (β = -0.173, p = 0.001), and PDEI (β = 0.119, p = 0.045). Performance (d' across both tasks) and overall confidence narrowly missed significance (β = -0.132, p = 0.063; β = -0.099, p = 0.056, respectively). *p < 0.05.

Regression model 3a – dependent variable: confirmatory PDEI; predictor variables: group (depressed/nondepressed), age, gender, performance (d'), and overall confidence.

Regression model 3b – dependent variable: disconfirmatory PDEI; predictor variables: group (depressed/nondepressed), age, gender, performance (d'), and overall confidence.

Regression model 4 – dependent variable: self-esteem; predictor variables: demographic variables (age, gender, education level), performance variables (d', objective evidence strength, performance at higher postdecision evidence) and metacognitive variables (meta-d', overall confidence, PDEI) (**Figure 5**).

A subset of covariates from model 1 was not included in models 2–3b after determining they were not associated with depression score. For completeness, we repeated the analysis of models 2–3b with the full set of covariates to ensure that all findings remained unchanged. We checked for multicollinearity of all multiple regressions by calculating the variance inflation factor for each predictor, which was <2 for all regressions and predictors and below a standard cutoff value of 10 (43).

Calculation of Confidence Bias and Metacognitive Sensitivity

Confidence bias was calculated as the mean confidence rating of all trials of the confidence task and reflects an individual's tendency to use higher or lower confidence ratings regardless of their performance.

To measure metacognitive sensitivity (the extent to which participants adjust their confidence judgments following correct or incorrect decisions) we calculated meta-d' (44). This is based on signal detection theory and is a standard metric for assessing metacognitive sensitivity (2). The advantage of using meta-d' is that it is not influenced by a person's general propensity to report their confidence as higher or lower.

To estimate meta-d' for each subject, we used a Bayesian estimation scheme (45) using the nonhierarchical version of the model.

Calculation of Postdecision Evidence Integration

PDEI was measured as the increase in confidence caused by postdecision (confirmatory) evidence when subjects were initially correct and the decrease in confidence caused by postdecision (disconfirmatory) evidence when subjects were initially incorrect. To this end, for each participant, we constructed a trial-by-trial linear model of data pooled across both tasks. In this model, confidence was the dependent variable, and the following predictors were entered: accuracy (correct = 1, incorrect = -1), postdecision evidence strength (confidence task = 0, low postdecision evidence = 1, high postdecision evidence = 2), and the critical accuracy × postdecision evidence strength interaction term. This interaction term quantifies the extent to which confidence increases on correct trials and decreases on error trials as postdecision evidence strength increases. This forms a summary measure of sensitivity to additional evidence (PDEI).

Depression Score and Self-Esteem Measure

Because of fewer participants scoring at the higher end of the depression questionnaire, we conducted a log linear transformation on depression questionnaire scores to reduce positive skew. This transformed variable was used for all subsequent analysis.

We used the arcsin transformation to reduce negative skew in our self-esteem scores, and this variable was used in all subsequent analyses.

RESULTS

Overall Performance and Confidence Reports

Following the staircase procedure (in which participants' performance was staircased to 71% accuracy), participants performed on average at 73.1% accuracy with a range of 60% to 84.9%.

Participants' mean confidence in their decisions on the confidence task (task 1) was 75.6% (SD = 0.11) when correct and 65.8% (SD = 0.12) when incorrect. Postdecision evidence (displayed in task 2) had the expected effect on confidence ratings. For correct choices, mean confidence increased to 75.8% (SD = 0.11) following low postdecision evidence strength and increased to 85.1% (SD = 0.11) following high postdecision evidence strength. For incorrect choices, confidence lowered to 53.4% (SD = 0.15) following low postdecision evidence strength and 38.4% (SD = 0.19) following high postdecision evidence strength. This shows that participants adjusted their confidence accordingly when shown further evidence after making their decision.

Overall Confidence, Metacognitive Sensitivity, and Depressive Symptoms

Depression as a Continuous Variable

First, we constructed a multiple linear regression model (Regression model 1; **Figure 2**) to assess whether depressive symptoms were associated with lower overall confidence and better metacognitive sensitivity.

The association between overall confidence and depressive symptoms narrowly missed significance (β = -0.099, p = 0.056), and it was further weakened when controlling for self-esteem (β = 0.009, p > 0.1).

There was no association between metacognitive sensitivity (meta-d') and depressive symptoms (β = 0.052, p > 0.1).

Depression as a Categorical Variable

Participants' depression scores ranged from 20 to 77, with an average score of 37.04. Using a cutoff of 50 [recommended by Ref. (40)], 57 participants (~14% of our sample) met criteria for at least mild depression. The mean depression score in the depressed group was 56.66 (SD = 6.21) and in the nondepressed group was 33.92 (SD = 8.07).

To investigate the difference in overall confidence between depression groups, we constructed a multiple linear regression model (Regression model 2). We found no significant association between group and overall confidence (p = 0.244) or any other variable (all p > 0.05).

Postdecision Evidence Integration and Depressive Symptoms

Depression as a Continuous Variable

We used the multiple linear regression reported above (Regression model 1; **Figure 2**) to also assess the relationship between PDEI and depressive symptoms.

PDEI was significantly associated with depression score (β = 0.119, p = 0.045), meaning that participants with higher depressive symptoms were more sensitive to new information, adjusting their confidence ratings to a greater extent.

Depression as a Categorical Variable

To investigate the difference in PDEI between groups, we conducted a linear regression (Regression model 3). Consistent with the analysis using depression score as a continuous variable, we found a significant positive association between PDEI and group (β = 0.124, p = 0.005). This confirms that after receiving postdecision evidence, depressed individuals adjust their confidence more than nondepressed individuals (**Figure 3**).

We then used linear regression to investigate PDEI separately for when participants received confirmatory or disconfirmatory evidence. First, we entered confirmatory evidence integration as the dependent variable (Regression model 3a). We found that group was positively associated with postdecision integration of confirmatory evidence (β = 0.094, p = 0.019), such that depressed participants exhibited a greater boost in confidence when receiving postdecision evidence after correct judgments. Second, we entered disconfirmatory evidence integration as the dependent variable (Regression model 3b). We found again that group was positively associated with postdecision integration of disconfirmatory evidence (β = 0.093, p = 0.033), such that

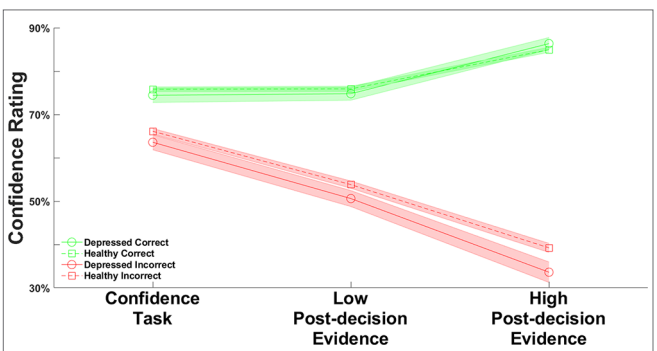

FIGURE 3 | Average confidence rating across the confidence and postdecision evidence integration (PDEI) tasks, separated by group. Green lines show confidence when participants were correct; red lines show confidence when participants were incorrect. Dotted lines indicate nondepressed participants (scoring less than 50 on the depression scale); solid lines indicate depressed participants (scoring at least 50 on the depression scale). The shaded areas indicate the standard errors of the mean. In linear regression analysis, we found a significant association between group (depressed/nondepressed) and PDEI (β = 0.361, p = 0.005).

depressed participants exhibited a greater reduction of confidence when receiving postdecision evidence after incorrect judgments. This indicates that the increased incorporation of postdecision evidence in depressed subjects is not a valence effect (e.g., depressed subjects only incorporating disconfirmatory evidence) but a general characteristic of postdecision processing.

To further visualize these associations, we binned data into five categories according to depression score (20–29, 30–39, 40–49, 50–59, and 60+). **Figure 4A**, **B** show the mean overall confidence and PDEI scores, respectively, across the five categories.

Sensitivity Analysis

When performing the analyses with depression as a categorical variable (models 2–3b), we did not include education or performance at the higher staircase value as predictors because they were not associated with depression score in regression model 1. However, for consistency with all other analyses in this study, we repeated these analyses with the full set of covariates (see regression model 1). This had little influence on the results: depression group was not associated with overall confidence (β = -0.059, p = 0.235), but it was associated with PDEI (β = 0.107, p = 0.015), both for confirmatory (β = 0.090, p = 0.025) and disconfirmatory (β = 0.079, p = 0.067) evidence.

Demographics, Performance Variables, and Depressive Symptoms

Using regression model 1, we could also investigate the relationship between depressive symptoms and demographics and performance variables. As expected, we found that age and gender were significantly associated with depressive symptoms (age β = -0.173, p = 0.001; gender β = -0.138, p = 0.008). Younger and female participants had higher depressive symptoms, consistent with a large body of prior work (46, 47).

There was a negative association between performance (d') and depression, which narrowly missed significance (r = -0.132, p = 0.063), underscoring the importance of controlling for this variable in the analyses. However, we note that this effect is in the opposite direction to the association found between depressive symptoms and PDEI. If depression was associated with a generalized insensitivity to evidence, then we would expect that more depressed individuals would perform worse and show less PDEI. On the contrary, despite the weak association with worse performance, we find that depression is associated with greater PDEI, suggesting a specific change in metacognitive evaluation that cannot be explained by performance differences.

Metacognitive Function and Self-Esteem

As expected, self-esteem was strongly negatively associated with depression scores (r = -0.678, p < 0.001).

To investigate the relationship between self-esteem and metacognitive function, we conducted a linear regression (Regression model 4; **Figure 5**).

Overall confidence was significantly positively associated with self-esteem (β = 0.203, p < 0.001). This effect remained significant when controlling for depression score (β = 0.109, p = 0.002). There were no significant associations between self-esteem and the other measures of metacognitive function (meta-d' p = 0.279 and PDEI p = 0.070).

We also found that age was a significant predictor of self-esteem (β = 0.106, p = 0.028), with younger participants scoring lower.

To further visualize these associations, we binned data into five categories according to self-esteem score (0–20, 21–40, 41–60,

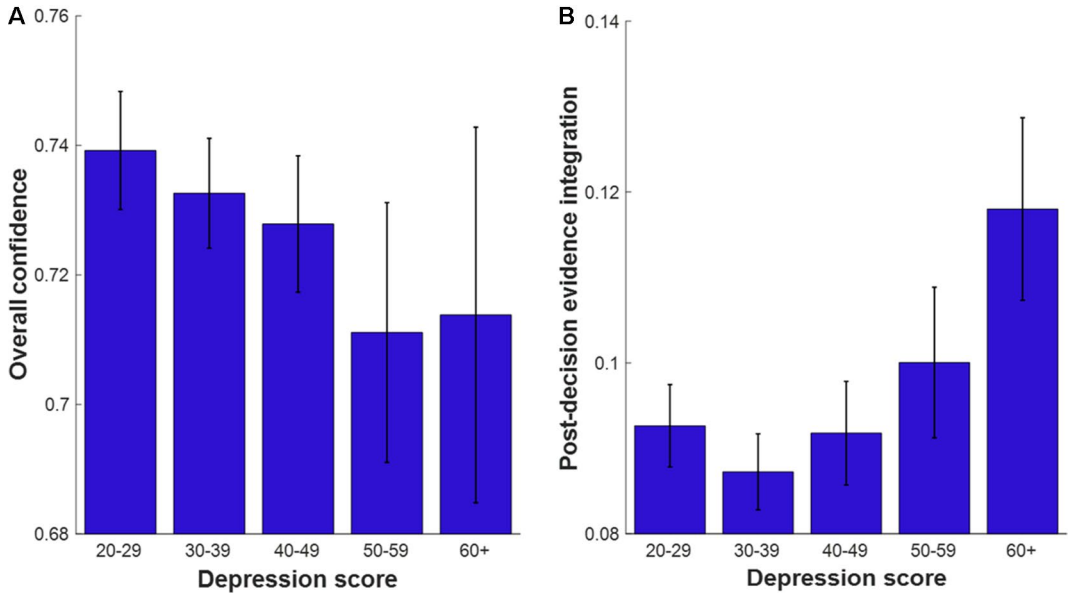

FIGURE 4 | Metacognitive variables plotted as a function of depression score in five bins (50 is the recommended cutoff classifying mild depression). Error bars indicate the standard errors of the mean. **(A)** Mean Overall confidence across depression bins. **(B)** Mean Postdecision evidence integration score across depression bins. Ns per bin: depression score 20–29 (n = 120), 30–39 (n = 135), 40–49 (n = 104), 50–59 (n = 41), 60+ (n = 16).

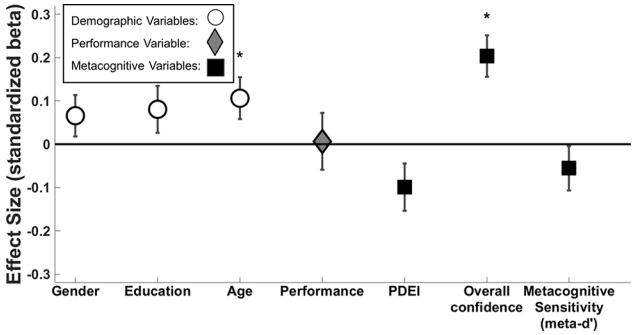

FIGURE 5 | Standardized beta coefficients (± standard error) of predictors of self-esteem score. White circle markers indicate demographic variables, the grey diamond indicates performance (d' across both tasks) and black squares indicate metacognitive variables. We demonstrate significant effects of age ($\beta = .106$, $p = .028$) and overall confidence ($\beta = .203$, $p = < .001$). *$p < .05$.

61–80, 81–100). **Figure 6A**, **B** show mean overall confidence and PDEI score, respectively, across the five categories.

DISCUSSION

In a large unselected online sample, we investigated the association between metacognitive function (overall confidence, metacognitive sensitivity, and PDEI), depressive symptoms, and self-esteem.

We identified a marginal negative association between depressive symptoms and overall confidence during perceptual decision making. However, when comparing depressed and nondepressed groups, we did not observe any significant difference in overall confidence. Thus, we observed only weak evidence for our first hypothesis, derived from Rouault et al. (21), that depressive symptoms would be associated with lower metacognitive confidence.

We also did not detect any significant association between depressive symptoms and metacognitive sensitivity (meta-d'), even though in the current data set, meta-d' and PDEI (which was associated with depressive symptoms, see below) are positively correlated (31). Thus, we did not confirm our second hypothesis that depressive symptoms would be associated with better metacognitive sensitivity.

Instead, depressive symptoms were associated with greater integration of postdecision evidence, meaning that more depressed participants adjusted their confidence more (i.e., they were more likely to change their mind) in the face of new evidence having made a decision. This pattern was also evident in a categorical analysis of depression: participants who met a threshold for at least mild depression had greater PDEI scores than participants scoring in the nondepressed range. Interestingly, the degree of PDEI was increased for both confirmatory and disconfirmatory evidence in depressed participants (albeit the association with disconfirmatory PDEI narrowly missed significance in a sensitivity analysis), indicating a generally heightened sensitivity to new evidence following a decision rather than a biased integration of negative information.

It is possible that the integration of postdecision evidence might act as a more sensitive experimental marker of self-evaluation than metacognitive sensitivity (meta-d'), which relies on endogenous fluctuations in confidence.

Our self-esteem measure was more closely related to differences in overall confidence than depressive symptoms.

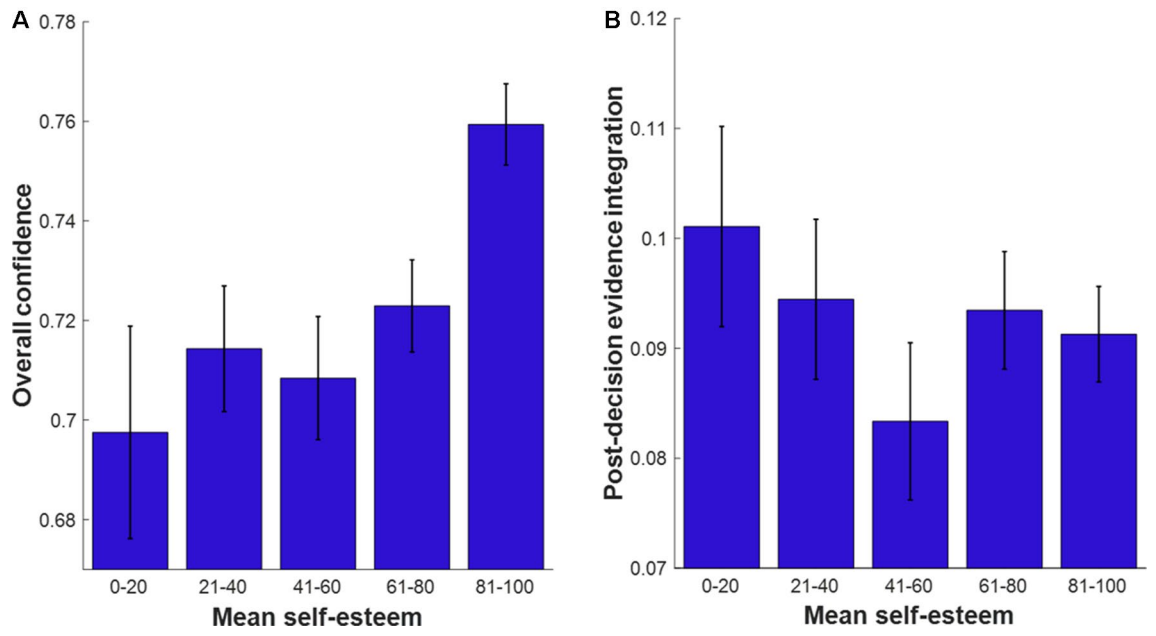

FIGURE 6 | Metacognitive variables as a function of self-esteem score in five bins. Error bars indicate the standard errors of the mean. **(A)** Mean overall confidence plotted as a function of self-esteem bins. **(B)** Mean postdecision evidence integration plotted as a function of self-esteem bins. Ns per bin: Self-esteem score 0–20 (n = 44), 21–40 (n = 59), 41–60 (n = 51), 61–80 (n = 111), 81–100 (n = 151).

Overall confidence was positively associated with self-esteem and, despite the correlation between depressive symptoms and self-esteem, this association remained significant when controlling for depression score. We did not observe a significant association between self-esteem and metacognitive sensitivity or PDEI.

Depressive Symptoms Were Associated With Greater Postdecision Evidence Integration

Depressed participants adjusted their confidence more in the face of new evidence, and this effect was exacerbated at higher evidence strengths. In our task, increased PDEI was adaptive and resulted in more accurate evaluations of participants' decisions. However, there was no association between depressive symptoms and earnings, arguing against the notion that depressed participants were simply more motivated to win money and thus adjusted their confidence more to try to do so. Instead, this pattern is consistent with a depressive realism account (8).

Another way to interpret PDEI is in terms of changes of mind. The study of postdecisional evaluation may pave the way toward an explanation of symptoms, such as indecisiveness. Interestingly, participants in the depressed group adjusted their confidence more both when they were correct (and received confirmatory postdecision evidence) and when they were incorrect (and received disconfirmatory postdecision evidence). This symmetry argues against an influence of valence in changes of mind, for example, an oversensitivity to disconfirmatory evidence or an inability to integrate confirmatory evidence.

Importantly, by adjusting their confidence more in the face of postdecision evidence, participants in the depressed group were performing better than participants in the nondepressed group. This shows the interesting complexities in understanding the mechanisms underpinning depressive symptoms—what appears as adaptive in one task may in fact lead to maladaptive decision making in other settings. However, further evidence is needed with more direct self-report measures of indecisiveness to disentangle the contribution of metacognitive confidence to this symptom.

Overall Confidence Was Better Explained by Self-Esteem Than Depressive Symptoms

We found a weak association between depression score and overall confidence that narrowly missed significance ($p = 0.056$) and was weakened when controlling for self-esteem ($p > 0.1$). Rouault et al. (21) found a significant association between depression score and overall confidence in experiment 1 but not in experiment 2. It is important to note, however, that the focus of the current study was on depressive symptomatology in isolation (as measured with the Zung scale), whereas in Rouault et al. (21), the strongest relationships with metacognition were observed for a factor that cross-cut elements of both anxiety and depression. Specifically, when using factor analysis to cluster symptoms independently of questionnaire of origin, Rouault et al. (21) found a strong association between their anxious–depression factor and overall confidence. This pattern of results raises the possibility that the lower confidence found in relation to greater anxious–depression factor scores in Rouault et al. (21) may be driven more by anxious than depressive symptoms.

Self-esteem showed a strong association with overall confidence in performance, as derived from the average of trial-by-trial ratings. This suggests that self-esteem may be closely related to concepts of self-efficacy (i.e., overall beliefs about self-performance). Notably, self-esteem was not related to either metacognitive sensitivity (meta-d') or PDEI, suggesting that it tracks overall beliefs about the probability of success, rather than affecting postdecisional monitoring. Future research should address whether this relationship occurs across multiple task paradigms, exploring different dimensions of self-esteem, for example, self-efficacy versus self-liking (48).

Limitations and Future Directions

Several limitations to this study merit comment. First, we recruited and tested participants from an unselected online sample. This meant that we recruited relatively few participants who scored over the cutoff for mild depression (cutoff score 50, ~14% of our sample), and the mean depression score of this group was quite mild ($M = 56.66$). Second, we were only able to obtain a single questionnaire measure of depressive symptoms (40) and a single-item measure of self-esteem (42) because of time constraints and concerns about sustained attention in online experiments (49). Finally, we were unable to identify participants who met clinical criteria for a major depressive episode using this scale (40). We also did not collect any details on previous episodes or comorbidities, life events leading up to the time of the experiment or current psychiatric treatment. It is possible, for instance, that people who have suffered negative shocks to self-efficacy (such as social or professional rejections) may have both higher depression scores and lower global metacognitive evaluations (21).

Therefore, future research should confirm these findings by comparing well-characterized clinically depressed patient populations with matched healthy controls. Collecting detailed psychiatric histories and measures of life events would allow the assessment of relationships between these variables and metacognitive measures. It would also be worthwhile to investigate symptom profiles in more detail to examine how specific symptoms (e.g., indecisiveness) relate to PDEI.

Participants in our study were given a monetary incentive to rate their confidence as accurately as possible. The monetary reward was calculated using a quadratic scoring rule that means that participants earn the most points when maximally confident and correct or minimally confident and incorrect. When comparing depressed and nondepressed groups, one possible concern is that this incentive might not have had the same value across the participants; for example, depressed participants might be less motivated to win money because of disrupted motivation. However, two factors lessen this concern: 1) depressed participants did not earn significantly less money than nondepressed participants; 2) our main finding that depressed participants adjusted their confidence more following further evidence (PDEI) would indicate that, if anything, depressed participants considered the accuracy of their confidence ratings more carefully than nondepressed participants.

Another potential concern is that this study was carried out as part of a replication experiment within a previous study on political attitudes (31), which could raise the Type I error rate because we did not correct for multiple comparisons in relation to the other questionnaires in the study (although here our focus was on associations with depressive symptoms, not political attitudes). Therefore, these results should be treated with caution until the study is independently replicated.

CONCLUSION

We have identified small but significant shifts in metacognitive function associated with higher depressive symptoms and lower self-esteem. We found some evidence that depressive symptoms were associated with lower overall confidence [as shown in Ref. (21)], but we were not able to replicate the finding that depressive symptoms were associated with greater metacognitive sensitivity (meta-d') (21). We found that depressive symptoms were associated with greater PDEI, and that a self-esteem measure was better able to account for differences in overall confidence than depression score. We were able to demonstrate this in a large sample of unselected participants recruited online, highlighting the potential of this method of recruitment in psychological experiments (50). However, this method inevitably has some limitations, particularly in relation to the characterization of symptoms. Future studies should examine PDEI in well-characterized patient populations with more comprehensive measures of symptoms.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Participants gave informed consent and the study was approved by the Research Ethics Committee of University College London (study number 1260-003).

AUTHOR CONTRIBUTIONS

All four authors designed the experiment and contributed to the writing of the manuscript. MR collected the data. MM-P analyzed the data and wrote the first draft of the manuscript.

FUNDING

The Wellcome Centre for Human Neuroimaging is supported by core funding from the Wellcome Trust (203147/Z/16/Z). S.M.F. is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (206648/Z/17/Z)

REFERENCES

1. Koriat A. Metacognition and consciousness. In Zelazo PD, Moscovitch M, Thompson E (Eds.), *The Cambridge handbook of consciousness*. New York, NY, US: Cambridge University Press. (2007). p. 289–325. doi: 10.1017/CBO9780511816789.012
2. Fleming SM, Lau HC. How to measure metacognition. *Front Hum Neurosci* (2014) 8:443. doi: 10.3389/fnhum.2014.00443
3. Fleming SM, Weil RS, Nagy Z, Dolan RJ, Rees G. Relating introspective accuracy to individual differences in brain structure. *Science* (2010) 329(5998):1541–3. doi: 10.1126/science.1191883
4. Lobitz WC, Post RD. Parameters of self-reinforcement and depression. *J Abnorm Psychol* (1979) 88:33–41. doi: 10.1037/0021-843X.88.1.33
5. Rozensky RH, Rehm LP, Pry G, Roth D. Depression and self-reinforcement behavior in hospitalized patients. *J Behav Ther Exp Psychiatry* (1977) 8:35–8. doi: 10.1016/0005-7916(77)90102-1
6. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* (1960) 23(1):56. doi: 10.1136/jnnp.23.1.56
7. Wallington SA. Consequences of transgression: self-punishment and depression. *J Pers Soc Psychol* (1973) 28:1–7. doi: 10.1037/h0035576
8. Alloy LB, Abramson LY. Judgment of contingency in depressed and nondepressed students: sadder but wiser? *J Exp Psychol Gen.* (1979) 108:441–85. doi: 10.1037/0096-3445.108.4.441
9. Beck AT. Beck depression inventory. *Depression* (1961) 2006:2–4. doi: 10.1093/ndt/gfr086
10. Beck AT. Cognitive models of depression, in Clinical Advances in Cognitive Psychotherapy: Theory and Application (New York, NY: Springer Publishing), 29-61. Available at: https://books.google.com/books?hl=en&lr=&id=IVLSCgAAQBAJ&oi=fnd&pg=PA29&dq=beck+cognitive+models+of+depression&ots=QHBsGuXfz6&sig=tea5YbVvfMP8Me3HyILGmF-V5gw#v=onepage&q=beck%20cognitive%20models%20of%20depression&f=false [Accessed August 27, 2019]
11. Beyer S. The effects of gender, dysphoria, and performance feedback on the accuracy of self-evaluations. *Sex Roles* (2002) 47:453–64. doi: 10.1023/A:1021600510857
12. Fu T, Koutstaal W, Fu CHY, Poon L, Cleare AJ. Depression, confidence, and decision: evidence against depressive realism. *J Psychopathol Behav Assess* (2005) 27:243–52. doi: 10.1007/s10862-005-2404-x
13. Szu-Ting Fu T, Koutstaal W, Poon L, Cleare AJ. Confidence judgment in depression and dysphoria: the depressive realism vs. negativity hypotheses. *J Behav Ther Exp Psychiatry* (2012) 43:699–704. doi: 10.1016/j.jbtep.2011.09.014
14. Wood J, Moffoot APR, O'Carroll RE. Depressive realism revisited: depressed patients are realistic when they are wrong but are unrealistic when they are right. *Cogn Neuropsychiatry* (1998) 3:119–26. doi: 10.1080/135468098396198
15. Dunn BD, Dalgleish T, Lawrence AD, Ogilvie AD. The accuracy of self-monitoring and its relationship to self-focused attention in dysphoria and clinical depression. *J Abnorm Psychol* (2007) 116:1–15. doi: 10.1037/0021-843X.116.1.1
16. Stone ER, Dodrill CL, Johnson N. Depressive cognition: a test of depressive realism versus negativity using general knowledge questions. *J Psychol Interdiscip Appl* (2001) 135:583–602. doi: 10.1080/00223980109603722
17. Hancock JA, Moffoot APR, O'Carroll RE. Depressive realism assessed via confidence in decision-making. *Cogn Neuropsychiatry* (1996) 1:213–20. doi: 10.1080/135468096396514
18. Quiles C, Prouteau A, Verdoux H. Associations between self-esteem, anxiety and depression and metacognitive awareness or metacognitive knowledge. *Psychiatry Res* (2015) 230:738–41. doi: 10.1016/j.psychres.2015.10.035
19. Mather PM. Cluster analysis for researchers. *Comput Geosci* (1992) 18:98. doi: 10.1016/0098-3004(92)90065-Y
20. Rosenberg M. Rosenberg's self-esteem scale. *Society and the adolescent self-image.* Priceton, NJ: Princeton University Press (1965).
21. Rouault M, McWilliams A, Allen MG, Fleming SM. Human metacognition across domains: insights from individual differences and neuroimaging. *Pers Neurosci* (2018a) 1, E17. doi: 10.1017/pen.2018.16.

22. Moran R, Teodorescu AR, Usher M. Post choice information integration as a causal determinant of confidence: novel data and a computational account. *Cogn Psychol* (2015) 78:99–147. doi: 10.1016/j.cogpsych.2015.01.002
23. Yeung N, Summerfield C. Metacognition in human decision-making: confidence and error monitoring. *Philos Trans R Soc B Biol Sci* (2012) 367(1594):1310–21. doi: 10.1098/rstb.2011.0416
24. Fleming SM, Daw ND. Self-evaluation of decision-making: a general bayesian framework for metacognitive computation. *Psychol Rev* (2017) 124(1):91. doi: 10.1037/rev0000045
25. Moreira CM, Rollwage M, Kaduk K, Wilke M, Kagan I. Post-decision wagering after perceptual judgments reveals bi-directional certainty readouts. *Cognition* (2018) 176:40–52. doi: 10.1016/j.cognition.2018.02.026
26. Resulaj A, Kiani R, Wolpert DM, Shadlen MN. Changes of mind in decision-making. *Nature* (2009) 461(7261):263. doi: 10.1038/nature08275
27. Van Den Berg R, Anandalingam K, Zylberberg A, Kiani R, Shadlen MN, Wolpert DM. A common mechanism underlies changes of mind about decisions and confidence. *Elife* (2016) 5, e12192. doi: 10.7554/eLife.12192
28. Fleming SM, Van Der Putten EJ, Daw ND. Neural mediators of changes of mind about perceptual decisions. *Nat Neurosci* (2018). doi:10.1038/s41593-018-0104-6
29. Murphy PR, Robertson IH, Harty S, O'Connell RG. Neural evidence accumulation persists after choice to inform metacognitive judgments. *Elife* (2015). doi:10.7554/eLife.11946
30. Navajas J, Bahrami B, Latham PE. Post-decisional accounts of biases in confidence. *Curr Opin Behav Sci* (2016) 11:55–60. doi: 10.1016/j.cobeha.2016.05.005
31. Rollwage M, Dolan RJ, Fleming SM. Metacognitive failure as a feature of those holding radical beliefs. *Curr Biol* (2018) 28(24):4014–21. doi: 10.1016/j.cub.2018.10.053
32. Uher R, Perlis RH, Henigsberg N, Zobel A, Rietschel M, Mors O, et al. Depression symptom dimensions as predictors of antidepressant treatment outcome: Replicable evidence for interest-activity symptoms. *Psychol Med* (2012). doi:10.1017/S0033291711001905
33. Beck AT. *Cognitive therapy of depression.* New York, NY: Guildford Press (1979).
34. Sowislo JF, Orth U. Does low self-esteem predict depression and anxiety? A meta-analysis of longitudinal studies. *Psychol Bull* (2013) 139:213–40. doi: 10.1037/a0028931
35. Orth U, Robins RW, Roberts BW. Low self-esteem prospectively predicts depression in adolescence and young adulthood. *J Pers Soc Psychol* (2008). doi:10.1037/0022-3514.95.3.695
36. Bandura A. *Self-efficacy*: the exercise of control. London: Macmillan (1997).
37. Coutinho S. Self-efficacy, metacognition, and performance. *N Am J Psychol* (2008) 10(1).
38. Vrugt A, Oort FJ. Metacognition, achievement goals, study strategies and academic achievement: pathways to achievement. *Metacogn Learn* (2008) 3(2):123–46. doi: 10.1007/s11409-008-9022-4
39. Zimmerman BJ. Self-efficacy: an essential motive to learn. *Contemp Educ Psychol* (2000) 25(1):82–91. doi: 10.1006/ceps.1999.1016
40. Zung W. Zung Self-Rating Depression Scale (SDS). *Arch Gen Psychiatry* (1965) 1:63–70. doi: 10.1007/978-1-4419-1005-9_101893
41. Staël von Holstein CAS. Measurement of subjective probability. *Acta Psychol (Amst)* (1970). doi:10.1016/0001-6918(70)90013-2
42. Robins RW, Hendin HM, Trzesniewski KH. Measuring global self-esteem: Construct validation of a single-item measure and the rosenberg self-esteem scale. *Pers Soc Psychol Bull* (2001) 27(2):151–61. doi: 10.1177/0146167201272002
43. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. *Qual Quant* (2007) 41(5):673–90. doi: 10.1007/s11135-006-9018-6
44. Maniscalco B, Lau H. Signal detection theory analysis of type 1 and type 2 data: meta-d′, response-specific meta-d′, and the unequal variance SDT model. *Consciousness and cognition* (2014) 21(1), 422–430. doi: 10.1007/978-3-642-45190-4_3
45. Fleming SM. HMeta-d: hierarchical Bayesian estimation of metacognitive efficiency from confidence ratings. *Neurosci Conscious* (2017) 2017(1), 1–14. doi: 10.1093/nc/nix007
46. Baxter AJ, Scott KM, Ferrari AJ, Norman RE, Vos T, Whiteford HA. Challenging the myth of an epidemic of common mental disorders: trends in the global prevalence of anxiety and depression between 1990 and 2010. *Depress Anxiety* (2014) 31:506–16. doi: 10.1002/da.22230
47. Stone AA, Schwartz JE, Broderick JE, Deaton A. A snapshot of the age distribution of psychological well-being in the United States. *Proc Natl Acad Sci* (2010) 107:9985–90. doi: 10.1073/pnas.1003744107
48. Owens TJ. Two dimensions of self-esteem: reciprocal effects of positive self-worth and self-deprecation on adolescent problems. *Am Sociol Rev* (2006) 59(3), 391–407. doi: 10.2307/2095940
49. Crump MJC, McDonnell JV, Gureckis TM. Evaluating amazon's mechanical turk as a tool for experimental behavioral research. *PLoS One* (2013) 8(3):e57410. doi: 10.1371/journal.pone.0057410
50. Rand DG. The promise of mechanical turk: how online labor markets can help theorists run behavioral experiments. *J Theor Biol* (2012) 299:172–9. doi: 10.1016/j.jtbi.2011.03.004
51. Rouault M, Seow T, Gillan CM, Fleming SM. Psychiatric symptom dimensions are associated with dissociable shifts in metacognition but not task performance. *Biol Psychiatry* (2018b) 84(6):443–51. doi: 10.1016/j.biopsych.2017.12.017

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: info@frontiersin.org | +41 21 510 17 00

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership