EXECUTIVE FUNCTIONS IN PSYCHIATRIC DISORDERS

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EXECUTIVE FUNCTIONS IN PSYCHIATRIC DISORDERS

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Executive Functions comprise a range of neuropsychological processes related to intentional behavior and cognitive control. There are several theoretical models defining and explaining the concept of Executive Functions. Most of these models consider that the term Executive Functions encompasses cognitive process as working memory, cognitive flexibility, inhibitory control and other complex functions as planning, problem-solving and abstract reasoning. Other models argue that motivational and emotional functions, such as affective decision-making, reside under the concept of Executive Function.

Much evidence supports how complex cognitive functions are related to the physiological activity of brain networks, including the frontal cortex and its connections with subcortical structures. Several psychiatric disorders related to impairment in these brain networks (eg., bipolar disorder, schizophrenia, ADHD, obsessive-compulsive disorder, and drug addiction) leading to deficits in Executive Functions. These cognitive deficits affect patients' everyday functioning, worsening the clinical course of the disease. For example, deficits in Executive Functions are related to suicide behavior in bipolar disorder patients. Furthermore, these deficits also relate to obesity, a lack of adherence to treatment and an underperformance in the workplace and educational settings.

The understanding of the role of deficits in Executive Functions, including its neurobiological basis, developmental trajectories, and relationship with clinical outcomes, is fundamental to improve clinical management of psychiatric patients.

This research topic includes 13 articles with interdisciplinary contributions related to the understanding of the deficits in Executive Functions and its relationship with clinical manifestations in psychiatric disorders.

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EDITORIAL
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Editorial: Executive Functions in Psychiatric Disorders

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Editorial on the Research Topic

Executive Functions in Psychiatric Disorders

There's no consensus concerning the definition of Executive functions (EFs), its components and neurobiological underpinnings. Nonetheless, despites of these theoretical disagreements, an essential characteristic of these cognitive processes is its relationship with the capacity to manage cognition, behavior, emotions, and direct the response to established goals.

Diamond (2013) proposes that EFs presents a hierarchical structure with three core processes sub-serving another more complex cognitive functions. According to Diamond, based on previous research of Miyake et al. (2000), the core executive functions are working memory, cognitive flexibility, and inhibitory control. These functions emerge early in development and are the foundation for the elaboration of the complex EFs as problem-solving, planning, reasoning, and abstract thinking. Diamond propositions is a prominent theoretical model but do not focus on issues such as the role of emotion, motivation, and another process like affective decision-making that are frequently considered as a component of executive functions. For example, some authors argued that there are at least two main types of EFs, cool executive functions, related to abstract thinking and hot executive functions more related to emotion and motivation (Zelazo and Carlson, 2012).

According to Johnson (2012), EFs are expected to be impaired in psychiatric disorders. Therefore, these patients usually present a great chance of prejudice in adapt to the demands of social, workplace, school, and other contexts. Deficits in executive functions are related to marital stress (Bouchard and Saint-Aubin, 2014), suicide (Malloy-Diniz et al., 2009), lack of adherence to treatment (Perez et al., 2016), and poor academic performance (Ribner et al., 2017). Therefore, the understanding of the relationship of executive functions and psychopathology is necessary to improve clinical management of psychiatric patients. The primary objective of this research topic, which includes 13 articles from 70 authors from several fields of knowledge, was just recently described in a series of studies about executive functions in psychiatric.

Considering the theoretical perspective, Kluwe-Schiavon et al. provide a comprehensive discussion revisiting traditional EFs definitions. Authors propose that it is necessary to transcend the hot and cool dichotomy, and consider EFs in a dynamic and dimensional perspective.

Most of the articles included in this research topic discussed the relationship between EFs and psychiatric conditions. Duijkers et al. presents a review examining the relationship between

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executive functions deficits and self-regulation in those patients who suffered by dual pathology (substance use disorder and at least a comorbid disorder). The authors stressed the need to include the executive function assessment and treatment in the clinical management of these patients. Still considering the relationship between substance use disorders and EFs, Witter et al. reports results reinforcing the knowledge about the relationship between impulsivity/risk taking behavior and cocaine use. Authors were also presenting an important result that risk decisions in cocaine users could be related to an underlying mechanism that impedes the learning from immediate mistakes.

Soraggi-Frez et al. presents evidence that working memory deficits is often presented in Bipolar Disorder even in the euthymic stage. Furthermore, authors argue that the hedonic detector, a new component of Baddley's Working Memory model is frequently deregulated interfering in the affective judgment of environmental stimuli and experiences. Caixeta et al. also discussed cognitive Deficits in Bipolar patients. In a study of cognitive deficits in elderly depressed bipolar patients, authors found that neuropsychological deficits are comprehensive including working memory, processing speed, inhibitory control, and cognitive flexibility impairment. Together, Soraggi-Frez et al. and Caixeta et al. add evidence to the scientific literature concerning executive functioning deficits in Bipolar Disorder independently of age and current affective status. Finally, still in the field of executive functions in mood disorders, Almondes et al. present an interesting report that in elderly the interaction between depression and sleep complains contributes to a worse performance in EFs Tasks.

Executive function deficits were also discussed in two other psychopathologies, schizophrenia and ADHD. Berger et al. studied the electrophysiological pattern of activation comparing healthy control and two groups of schizophrenic patients (clustered according to the predominance of positive or negative symptoms) during a working memory task. The results point to a different pattern of frontoparietal activities both comparing health × clinical groups and positive × negative schizophrenic groups. These results could be relevant to the understanding of the nature of working memory deficits in schizophrenic patients. Martinez et al. discussed the overlap between executive functioning in ADHD and Post Traumatic Stress Disorder presenting data concerning the overlap between neural mechanisms subserving executive functioning in those disorders.

In a developmental perspective, Zebdi et al. discussed the interaction between environmental influences, mainly parent-child relationships, and the development of the executive functioning and internalizing symptoms. The authors point to the importance of a research agenda exploring the interaction between those above cited factors. Medeiros et al. described executive functioning deficits in both aggressors and victims of Bullying. While aggressors seem to have deficits in hot executive functions, victims seem to be more impaired in cool executive functions. These differences are important to both comprehensions and to the prevention of the phenomena.

Concluding this research topic, three articles present data, which are directed to clinical practices. Considering assessment issues, Sediyama et al. showed psychometric properties of the Brazilian Version of the UPPS Impulsive Behavior Scale, the tool used to evaluate components of impulsivity. Venza et al. and Hadwin and Richards presented evidence of successful intervention to improve executive functions and another cognitive process in psychiatric patients. The former article present results of a cognitive training program, focused in reasoning stimulation, in a sample of adult bipolar patients. The later, present the result of a computer working memory training program used in a sample of adolescents with the high level of anxiety.

As proposed initially, this research topic presented a heterogenic scope including both theoretical and applied issues concerning executive functioning in psychiatric disorders. Far from offering an exhaustive exploration of the topic, we hope to present here some specific contributions on the state of the art of this essential theme.

AUTHOR CONTRIBUTIONS

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

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REFERENCES

Bouchard, G., and Saint-Aubin, J. (2014). Attention deficits and divorce. *Can. J. Psychiatry* 59, 480–486. doi: 10.1177/070674371405900904

Diamond, A. (2013). Executive functions. *Annu. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

Johnson, M. H. (2012). Executive function and developmental disorders: the flip side of the coin. *Trends Cogn. Sci. (Regul. Ed).* 16, 454–457. doi: 10.1016/j.tics.2012.07.001.

Malloy-Diniz, L. F., Neves, F. S., Abrantes, S. S., Fuentes, D., and Corrêa, H. (2009). Suicide behavior and neuropsychological assessment of type I bipolar patients. *J. Affect. Disord.* 112, 231–236. doi: 10.1016/j.jad.2008.03.019

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Perez, K. M., Patel, N. J., Lord, J. H., Savin, K. L., Monzon, A. D., Whittemore, R., et al. (2016). Executive function in adolescents with

type 1 diabetes: relationship to adherence, glycemic control, and psychosocial outcomes. *J. Pediatr. Psychol.* 42, 636–646. doi: 10.1093/jpepsy/jsw093

Ribner, A. D., Willoughby, M. T., Blair, C. B., and Family Life Project Key Investigators (2017). Executive function buffers the association between early math and later academic skills. *Front. Psychol.* 8:869. doi: 10.3389/fpsyg.2017.00869

Zelazo, P. D., and Carlson, S. M. (2012). Hot and cool executive function in childhood and adolescence: development and plasticity. *Child Dev. Perspect.* 6, 354–360. doi: 10.1111/j.1750-8606.2012.00246.x

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Balancing Automatic-Controlled Behaviors and Emotional-Salience States: A Dynamic Executive Functioning Hypothesis

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Recently, there has been growing interest in understanding how executive functions are conceptualized in psychopathology. Since several models have been proposed, the major issue lies within the definition of executive functioning itself. Theoretical discussions have emerged, narrowing the boundaries between "hot" and "cold" executive functions or between self-regulation and cognitive control. Nevertheless, the definition of executive functions is far from a consensual proposition and it has been suggested that these models might be outdated. Current efforts indicate that human behavior and cognition are by-products of many brain systems operating and interacting at different levels, and therefore, it is very simplistic to assume a dualistic perspective of information processing. Based upon an adaptive perspective, we discuss how executive functions could emerge from the ability to solve immediate problems and to generalize successful strategies, as well as from the ability to synthesize and to classify environmental information in order to predict context and future. We present an executive functioning perspective that emerges from the dynamic balance between automatic-controlled behaviors and an emotional-salience state. According to our perspective, the adaptive role of executive functioning is to automatize efficient solutions simultaneously with cognitive demand, enabling individuals to engage such processes with increasingly complex problems. Understanding executive functioning as a mediator of stress and cognitive engagement not only fosters discussions concerning individual differences, but also offers an important paradigm to understand executive functioning as a continuum process rather than a categorical and multicomponent structure.

Keywords: executive functions, cognitive control, self-regulation, neuropsychology, automatic process, reasoning, stress, psychological

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INTRODUCTION

The conceptualizations of executive functions have emerged from the observation of patients who had suffered frontal lobe lesions and became unable to manipulate, integrate, and respond to internal and external stimulus in the same way they used to do (Jurado and Rosselli, 2007; Goldstein et al., 2014). Throughout the last few decades, a range of models have emerged and

executive functions has become a multifaceted mental concept that includes more than 30 different components (Barkley, 2001, 2012). Although these components were assumed to be interrelated, their exact relationship has not been clearly elucidated. After more than 40 years of studies, there is no consensus regarding the definition of executive functions. The concept previously included a variety of behaviors that were broadly accepted as "high-order cognitive processes," such as inhibitory control, attention shifting, working memory, goal-directed behavior, and strategic planning [for an extended review of definitions please see (Goldstein et al., 2014)].

Based upon recent neuroscientific findings and theories of cognitive sciences, this article questions this hierarchical characteristic, as well as the multicomponent categorical approaches, commonly attributed to executive functions, by presenting a novel and testable dynamic executive functioning hypothesis. Consequently, different from the majority of reviews on this topic (Miyake et al., 2000; Collette et al., 2005; Jurado and Rosselli, 2007; Tirapu-Ustarroz et al., 2008a,b; Kluwe-Schiavon et al., 2012; Goldstein et al., 2014), it is not the aim of this article to perform an updated overview concerning the theoretical models of executive functions, nor discuss current evidences for the reliability of unitary or multiple components models, and we do not aim to describe the subcomponents that were mostly accepted as "executive".

In order to accomplish our goal, the article is organized into three sections. In the first section, we briefly discuss the hierarchical and categorical framework that supports the majority of the models of executive functions, especially dual-processing models. In the second section, we highlight a selection of neuroscientific evidences to discuss stress as a core factor behind executive functioning phylogeny, particularly, that stress should be included in executive functioning models as a continuous variable leading to different levels of homeostasis disturbance and, as a consequence, cognitive engagement. The third section introduces the executive functioning hypothesis, elucidating similarities and differences between this perspective and some of the current theoretical models in the field. In this section, we also discuss that the so-called "executive" behaviors (e.g., set-shifting, cognitive flexibility, inhibition, and updating) that could be comprehended as consequences of a permanent adaptive switching between reflexive, conditioned, and goal-oriented behaviors, instead of core individual, but interrelated, cognitive components. Finally, the fourth section of the article discusses subsequent testing of our executive functioning hypothesis and future perspectives.

THE HIERARCHICAL FRAMEWORK OF EXECUTIVE FUNCTIONS

In an extensive review regarding executive functions, Goldstein et al. (2014) clarified that the first hypotheses concerning the role of prefrontal cortex (PFC) in human cognition were based upon the theoretical backgrounds of selective attention and multi-store memory models. These models suggested different linear schemas, such as the Bottleneck theory of attention from Donald Broadbent or the three component model from Richard Atkinson and Richard Shiffrin, in order to explain how environmental information are perceived, buffered, and retrieved for conscious awareness (Atkinson and Shiffrin, 1971; Goldstein et al., 2014). Although these models were able to distinguish automatic and controlled cognitive processes, they did not completely explain how information could be deliberatively selected or inhibited during demanding attentional tasks. To fill this gap, the term "cognitive control" was introduced in Posner and Snyder (1975) to describe the capacity to manage thoughts and emotions, allowing people to adapt behaviors across situations according their goals (Goldstein et al., 2014).

Together with previous studies from Alexander Luria, these dual-processing models – and subsequent models, such as the Supervisory Attentional System (SAS) from Norman and Shallice (1983) – were crucial to including the PFC as the main brain structure involved in cognitive control, which was capable of managing and regulating automatic behaviors (Luria, 1970; Norman and Shallice, 1983).

The differences between automatic and controlled processes driven by the cognitive revolution in psychology [for a review, please see (Miller, 2003)] favored a hierarchical and categorical approach, in which cognitive processes were organized as independent, but inter-related components according to their main functions, and aimed to decode the information processing pathway between a stimulus and behavioral response. The multicomponent working memory model proposed by Alan Baddeley and Graham Hitch (Baddeley, 2012) could be viewed as an example of this hierarchical and categorical reasoning, in which three distinct slave systems are coordinated by a central executive. However, according to Baddeley (2012), even though the central executive is the most complex component of working memory, it could be seen as a homunculus that represents a marker of issues requiring explanation. Although Baddeley (2012) suggested that in due course the homunculus might be pensioned off, several models remain convinced that the PFC is the "final frontier of neuropsychology" at the "center of human nature" (Stuss, 2011), and that executive functions "are at the heart of all socially useful, personally, enhancing, constructive, and creative activities" (Lezak, 1982). In other words, hierarchical and categorical approaches have often referred to executive functions as a homunculus that inhibits our instincts and guides our rational behavior.

This categorical approach can be widely observed in the executive functions multicomponent models. Examples include the four-component model hypothesized by (Lezak, 1995), as well as the three core functions summarized by Diamond (2013). The four-component model suggests that executive functions consist of those capacities that enable a person to engage successfully in independent, purposive, and self-serving behavior (Lezak et al., 2012), such as volition, planning, purposeful action, and effective performance (Goldstein et al., 2014). Similarly, Diamond (2013) suggested that executive functions can be described as a family of top down mental processes recruited when automatic, instinct or intuition would be insufficient to cope with an ongoing demand. Diamond relies upon the assumption that there is a general agreement regarding three core

executive functions: behavioral/cognitive inhibition (including selective attention), working memory, and cognitive flexibility (Diamond, 2013). These functions encourage individuals to not act impulsively, hold information to solve problems, and apply different approaches to a problem when facing new rules or priorities (Diamond, 2013).

In general, both models were based upon clinical experience and observation and they became expressive frameworks in the neuropsychological field. According to our perspective, the three main contributions of these models are: (i) hierarchical and multicomponent approaches make it easier to define some behaviors that seem to represent cognitive processes that could not be classified as general automatic responses caused by a stimulus (e.g., planning and cognitive flexibility); (ii) the possibility to develop specific tasks to assess each component independently (even theoretically considering that they are interrelated), which fits with one of the main aims of neuropsychology as a clinical field, to assess and treat patients with brain injury or disease; and (iii) the possibility to provide an explanation as to how executive dysfunction affects all aspects of behavior differently from specific cognitive deficits (Lezak et al., 2012). However, multicomponent models of executive functions are still based upon the traditional framework of "cognitive control" proposed by Posner and Snyder (2004), in which the PFC plays an "executive" role over goal-oriented behaviors (Pribram, 1973) and emotional self-regulation (for a review on this topic please see (Peterson and Welsh, 2014). To explain such control medical imaging technologies, developmental research, experimental psychology, and neurosciences have rescued dual-processes theories to describe the so-called "cold" and "hot" cognitive information processing systems (Sahlin et al., 2010; Zelazo and Carlson, 2012).

Once more, many dualistic models have been proposed to characterize these systems for an extensive review see (Evans, 2008). Usually, System 1 (or Type 1) demands stronger activation of subcortical structures and could be defined as unconscious, rapid, automatic, and allowed parallel information processing; while System 2 (or Type 2) demands stronger activation of cortical structures and could be defined as conscious, slow, deliberative, and mostly responsible for serial information processing (Kahneman, 2011; Noël et al., 2013). The idea of an "emotional versus rational" thinking or neural system has found support in several studies and has been extensively used to describe cognitive changes associated with psychiatric disorders and/or neurodevelopment. Some inhibition dysfunction theories of addiction, for example, suggest that chronic drug use reduces self-control, which is needed to inhibit the hedonic impulse to take the rewarding drug again [for a review about models of addiction please see (Emcdda, 2014)]. According to the dual-processing framework of addiction, the neuroplasticity induced by addictive drugs triggered by epigenetic mechanisms impacts proteins in an intracellular level, modifying neurotransmitter signaling in various neuronal circuits leading to an imbalance between those areas that are associated with emotions and reward (e.g., orbitofrontal cortex, ventral striatum, and the limbic system) – usually recruited during situations with stronger affective salience (e.g., facing conditioned drug cues or stress) – and those areas that are associated with more purely cognitive processing and the activation of the dorsolateral parts of the PFC (Volkow and Baler, 2014). Moreover, the imbalance between "hot" and "cold" brain systems has also been used to describe and explain risk-taking behaviors during adolescence, such as unprotected sex, criminal behavior, drug use and abuse, and accidents (Gladwin et al., 2011). Beyond social and environmental factors, neurodevelopmental researchers emphasized that the relatively early maturation of the "hot" affective-motivational bottom-up system and the more slowly developing "cold" top-down control system could explain impulsive behaviors due to the difficulty in delaying gratification (Benningfield et al., 2014), weighing of risks and benefits of a set of actions (Pripfl et al., 2013), and use of ongoing outcomes of these actions to monitor their own performance (Kluwe-Schiavon et al., 2016).

Although dual-process models have explained important issues, especially regarding decision-making, there are studies suggesting that these models might be outdated (Reyna and Brainerd, 2011; Gladwin and Figner, 2014). First, some authors argue that dual-processing models cannot supply and predict mechanisms for developmental reversals in cognition during development, such as increased reasoning biases from childhood to adulthood (Kahneman and Tversky, 2000; Reyna and Brainerd, 2011). Second, the boundaries between "hot" and "cold" executive functions are not clear and, considering previous theories regarding cognitive automaticity, it is not even clear if there are such boundaries (Bargh, 1992; Moors and De Houwer, 2006). Consequently, it became hard to investigate how individual factors (e.g., personality traits or mood), developmental factors (e.g., age and life experiences) and/or contextual factors (e.g., healthy or financial decisions and social interactions) – could influence the "warmth" of a task (Peterson and Welsh, 2014), thus requiring research to use decompositional approaches (Moors and De Houwer, 2006). In fact, it is true that earlier dual-processing models argued that a process is neither fully controlled nor automatic (Bargh, 1992). Despite many studies have discussed that "hot" and "cold" executive functions are supported by an integrated neural network, and, therefore, might be all interrelated (Zimmerman et al., 2016), in practice current studies still assume significantly different concepts. Finally, the third point is that dualistic conceptions (as well as the central executive homunculus of Baddeley) were thought to be didactically used to describe and explain complex behaviors. However, the exception has become the rule and these dualistic conceptions are replicated and measured as two independent categories instead of two poles of the same gradient. In other words, it is acceptable that "cold" executive functions are measured with tasks that demand planning, working memory, and concept formation, while "hot" executive functions are measured with tasks that demand social cognition, empathy, and emotion regulation (Zimmerman et al., 2016). In the next section we briefly highlight a selection of studies that support the idea that an executive functioning model should be thought of as a frontal-subcortical circuit, in which emotions (here stress) directly modulate the cognitive processes and vice-versa.

NEUROSCIENTIFIC FINDINGS TOWARD EXECUTIVE FUNCTIONING

The idea that executive functions are not exclusive related to frontal-cortical areas, but would involve frontal–subcortical neuronal circuits is not new (Leh et al., 2010). Based upon an evolutionary perspective, Ardila (2008) emphasized that executive functions are mediated by dynamic and flexible neuronal networks, questioning the central role of PFC in the executive functions and, afterward, discussing how the executive functions may have evolved in our species. Nonetheless, questioning the central role of PFC in relation to executive functions goes beyond suggesting that executive functions involve subcortical networks, but in fact this also allow us to question the hierarchical perspective in which PFC exerts control over impulses and should be taken as the center of rationality. Note that we do not intend to argue here that the PFC does not exert a key role in cognitive and response inhibition, but that there are enough evidences suggesting that the relationship between cognition and emotion could be more complex than the old-fashioned reasoning that the first (e.g., central executive, superego, or PFC) should control the second (e.g., impulses, id, or limbic system). In this sense, here we focus on those studies which suggested that some level of stress is necessary to motivate the organism to act and allocate cognitive resources to controlled processes, such as problem solving, monitoring, and updating. After a certain level of stress, the cognitive resources are reallocated in favor of more automatic processes, decreasing working memory span and, in the last instance, increasing response inhibition and unconditioned behaviors, such as fight or flight responses. Additionally, we mainly focus upon acute stress research since in the biological and psychological fields the term has been commonly used to describe external events capable of disrupting organism stability or homeostasis.

The executive functioning hypothesis is supported by studies that suggest that the PFC, especially medial areas, coordinates the brain circuits that mediate emotional responses (Hermans et al., 2014; McKlveen et al., 2015). This idea was deeply investigated under the somatic marker hypothesis, which demonstrated that the ventromedial PFC and its projections to the orbitofrontal cortex are involved in both emotional response and cognition (Bar-On et al., 2003; Li et al., 2010). The somatic marker hypothesis suggested that body signals (somatic markers) are represented and regulated in the ventromedial PFC, since these somatic markers were not found in people with lesions in this area, which are also correlated with poorer performance on decision-making tasks (Dunn et al., 2006). Additionally, the orbitofrontal cortex is known to show an increased activity in response to stress and it also is implicated in many cognitive functions, such as working memory. In this sense, pre-clinical research has hypothesized that acute stress can enhance working memory performance by selectively increasing glutamatergic signaling in PFC pyramidal neurons (Yuen et al., 2009). However, the extent to which stress can have a positive or negative effect on specific cognitive functions remains unclear. Barsegyan et al. (2010), for example, demonstrated that acute stress triggers working memory impairment and concurrent enhancement of memory consolidation. Interesting, the authors emphasized the interaction of glucocorticoid receptors and catecholaminergic activity, suggesting that working memory impairment and enhancement of memory consolidation shared a common neural influence within the medial PFC via a common activation of the noradrenergic signaling pathway (Barsegyan et al., 2010).

These data reinforce the idea that the medial PFC is an important integrator of the neuroendocrine and autonomic systems, acting as a coordinator of stress responses. In addition, these data also indicate that stress can be considered as a stimulus that allocates energetic systems to respond to an ongoing or anticipated challenge. McKlveen et al. (2015) discussed that this allocation of energetic systems may occur mostly via hypothalamic-pituitary-adrenal axis (HPA-axis) activation that culminate in the release of glucocorticoids and catecholamines, which in turn leads to several alterations in different brain systems in order to promote adaptive behaviors. As an example of allocation of energy systems, Hermans et al. (2014) have shown that acute stress shifts the phasic activation of locus coeruleus toward a tonic mode of activity, guiding attentional resources for potentially salient information. This allocation of energy resources could explain different behavior patterns observed during stress.

In this regard, two meta-analyses were performed to investigate the effects of psychosocial stress on executive functions (Shields et al., 2016) and the effects of stress on decisions made under uncertainty (Starcke and Brand, 2016). In the first, the authors found that acute stress impaired working memory and cognitive flexibility in humans. Furthermore, Shields et al. (2016) suggested that within inhibition, stress impaired cognitive inhibition (selectively attending to or ignoring information) but enhanced response inhibition. Concerning decision-making, Starcke and Brand (2016) found that stress had significant effects only in those situations in which increased reward seeking and risk taking is disadvantageous and discussed that this finding could be explained by two mechanisms: the first suggests that acute stress should increase the reliance on immediate and high rewards via alterations in dopamine release at the cost of considering potential losses; while the second mechanism suggests that stress may lead to unsystematic decisions without considering all of the options and may generally impair executive control via reductions of prefrontal functioning (Shields et al., 2016). Taken together, their findings are in agreement with the current perspective that stress reallocates limited executive resources in adaptive ways to facilitates adaptive decisions, although the authors highlight that it is not clear what executive function receives these reallocated resources and why (Shields et al., 2016).

It is also hypothesized that stress-induced shifts in cognitive functions occur because two different large-scale neuronal networks (salience network and executive control network) may

compete for limited resources, and as proposed by Hermans et al. (2014), regulate externally directed attention. This model goes further than the majority of "hot" and "cold" dualistic perspectives because it introduces a dynamic interaction between the delay between stressor onset and task performance, and also because it considers the prefrontal areas as the key structures supporting this "competition." In a second meta-analysis, Shields et al. (2015) investigated the effects of acute cortisol administration on executive functions, focusing upon working memory inhibition and set-shifting shifting. After separating the genomic effects of cortisol (slow-acting effects caused by the modulation of gene expression) from its non-genomic effects (rapid-acting effects without the modulation of gene expression) by controlling for the delay between cortisol administration and cognitive testing, the authors found interesting and divergent effects of the hormone in cognition according to different time-windows post-administration. The authors suggested that the non-genomic effects of cortisol significantly impair working memory between 15 and 73 min post-administration, but begins to improve working memory after this period. However, the same effects of cortisol improve inhibition from 15 to 135 min post-administration, but begins to impair inhibition after this period, and no effects where found related to set-shifting (Shields et al., 2015). This data is in accordance with the idea that stress levels modulate the allocation of cognitive resources in a dynamic perspective, increasing inhibitory control and decreasing working memory capacity, which we hypothesized could facilitate the organism to engage in a logic deliberative reasoning to solve the problem. Nevertheless, if this strategy was not sufficient to solve the problem, individuals might use the working memory as an automatic adaptive cognitive mechanism to guide behavior, demanding less logic deliberative reasoning. Moreover, this meta-analysis emphasized that the time course difference between salience network and executive control network to reach the peak and then return to the baseline could also be an important feature to comprehend different effects of stress in the executive functions. In the acute phase, neural resources are allocated toward the salience network and the executive control network is actively suppressed, while in the recovery phase, this effect is reversed.

Here we argue that, at a primary level, a minimum amount of stress is required in order to motivate the organism to act and cognitively engage in problem solving by decreasing working memory capacity. Unfortunately, there are few studies directly investigating these effects and the majority of evidences in this direction are based upon clinical studies suggesting that stress could decrease the threshold to act. For example, some authors suggest that schizophrenia is primarily a frontostriatal disorder (Liu et al., 2011), in which executive functions deficits and deterioration are a central aspect of the disease [for a review see (Kluwe-Schiavon et al., 2013)]. In this sense, recent findings in schizophrenia have reconceptualised context processing as a function of proactive and reactive cognitive control (Aron, 2011). Proactive control can be comprehended as a form of default mode activated by goal-relevant information before the occurrence of cognitively demanding events, to optimally bias attention, perception, and action systems in a goal-driven manner; while reactive control is recruited only after the detection of a high-interference event, favoring attentional control and response inhibition (Anticevic et al., 2013). The proactive control depends upon the updating and maintenance of contextual information, which in turn, are associated with Gamma-aminobutyric Acid (GABA) and glutamate neurotransmitter mechanisms and *N*-methyl-$_{D}$-aspartate (NMDA) receptor functioning. There are evidences suggesting that in schizophrenia, the connectivity between dorsolateral PFC and other cognitive control related brain regions are associated with dopamine and GABAergic signaling impairments, which support the information representation in dorsolateral PFC (Barch and Ceaser, 2012). Thus, such dysfunction in dopamine and GABAergic signaling may explain, in part, some of the behavior difficulties observed in schizophrenia related to proactive control, such as engaging in a conversation or planning. The notion of proactive control fits an executive functioning perspective because when facing a minimum level of stress, patients diagnosed with schizophrenia may have difficulties in allocating executive functioning resources necessary to properly engage in adaptive behavior.

Therefore, it seems unlikely that a "hot" vs. "cold" dichotomy will remain as a source of hypotheses for research in cognitive and experimental neuroscience. Although these dual-processes models have contributed to the understanding of information processing and brain disorders (Volkow and Baler, 2014), research questions centerd upon a categorical epistemological base seem to defy recent findings in the field (Morris and Cuthbert, 2012). Current interdisciplinary efforts to integrate "hot" and "cold" processes is timely and important since psychological scientists have previously assumed that adaptive behavior in real-world contexts involves continuous interactions between emotional and cognitive processes (Peterson and Welsh, 2014).

Taken together, our main goal here is to highlight that although the literature converges toward a dynamic role of PFC as a coordinator of stress adaptation, executive functions literature appears to be mostly focused upon hierarchical and categorical approaches. More than inter-related components that exert control over emotional salience, we propose that executive functioning should be comprehended as the main processes behind the allocation of cognitive resources in the face of a challenge. In this sense, instead of looking for energization, one can investigate the amount of stress that is needed to motivate the organism to act; instead of looking for problem solving or inhibitory control, one can investigate how long the organism can keep the executive control network engaged without shifting energy resources for working memory and salience network during a mild, moderate, or severe stress challenge. Instead of looking for cognitive flexibility, one can investigate how fast the organism can retrieve and adapt conditioned behavior schemas to cope with a new scenario. This dynamic perspective considers executive functioning as continuum process that could be used to identify how adaptable the organism is to an unpredictable environment.

A DYNAMIC EXECUTIVE FUNCTIONING HYPOTHESIS

Our dynamic executive functioning hypothesis emerged from a fundamental question raised by Barkley (2001), "Why did humans develop executive functions?" Taking an evolutionary perspective, we argue that executive functioning emerged from: (a) the ability to solve immediate problems and generalize successful strategies; and (b) the ability to synthesize and organize environmental information in view of identifying uniformities that allow predictions about nature and future. From our perspective, these abilities are intrinsically related with two fundamental assumptions that are omitted by the majority of executive functions models. The first is a motivational feature that refers to the necessity of an existent problem to be solved, in other words, a motivational variable that might stress the organism and instigate the goal-oriented behavior. The second refers to the optimization of future solutions based upon previous experience, which is an ontogenetic assumption based upon the combination of the ability to generalize successful strategies along development and the ability to predict problems. The first assumption instigates the necessity to include a motivational variable derived from an internal or external stressful event capable of disturbing the organism homeostasis. Thus, this motivational aspect should be comprehended as a continuum that represents levels of homeostasis disturbance. The second assumption suggests that executive functions could be considered a "cyclical" process (that is why we refer to it as executive "functioning"), in which the main goal is to automatize efficient solutions that were cognitively demanding in the past, enabling individuals to allocate cognitive resources to the executive control network to solve new complex problems.

Here we proposed a schematic model to illustrate that the executive functioning could be comprehended as a balance between the salient network and the executive control network (**Figure 1A**). Differently from the majority of dual-processing models in which the strongest activation of salient network necessarily culminates in the weakness of cognitive executive control network, our theoretical hypothesis suggests that the strength and the direction of the relationship between these two networks would be indicative of optimal or impaired executive functioning. In optimal executive functioning, the organism

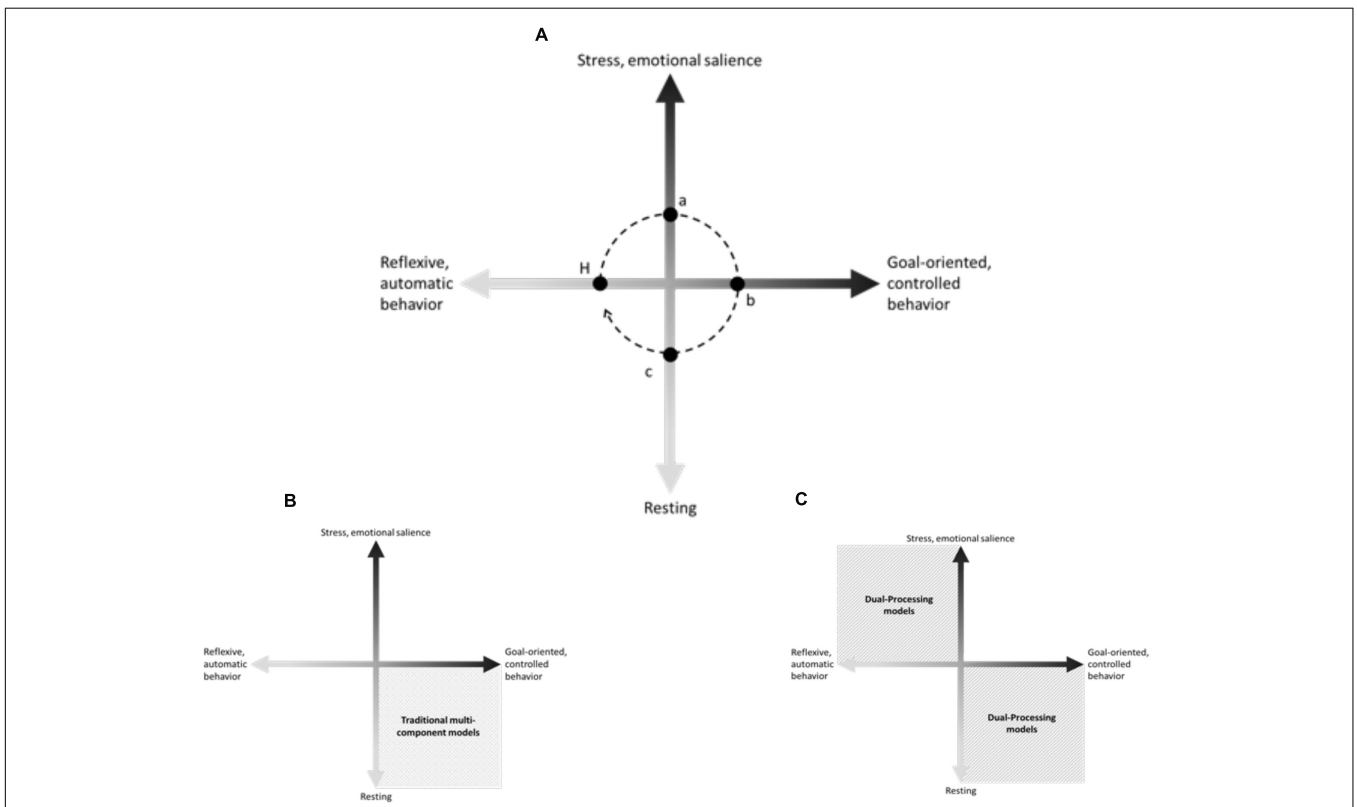

FIGURE 1 | Dynamic executive functioning hypothesis. (A) Dynamic executive functioning hypothesis: our theoretical hypothesis suggests that organisms tend to maintain a homeostatic state (H). Stress occurs, when any environmental demand gradually triggers goal-oriented behaviors, firstly using habitual responses and adapting it to adjust to the new demand. In an optimal executive functioning, when the ongoing behavior is insufficient to respond to environmental demands the emotional salience network reaches a peak (a), the organism would be able to inhibit disruptive automatic behaviors such as fight or flight responses and to use the available information (emotional salience and previous behaviors) to successfully respond to the environmental demand, decreasing the emotional salience and decoding the new contingencies (b). Once the new contingencies are decoded, the organism would repeatedly use the successful behavior (c) to completely solve the environmental demand and, then, returning to the homeostatic state (H). **(B)** Traditional multicomponent models. **(C)** Dual-processing models.

should be able to quickly adjust the ongoing behavior when faced with a stressful event. To do so, the organism should retrieve previous successful strategies and should be flexible enough to adapt these strategies if necessary. The executive functioning lies in the amount of stress necessary to motivate problem solving and the amount of cognitive effort demanded to solve the problem. If the organism is not sufficiently sensitive to identify potentially stressful events and to initiate an adaptive response in time, this would suggest a failure in updating environmental information. If the problem-solving demands a greater amount of cognitive effort that does not correspond to the difficulty level of the task, this results in a failure in monitoring the ongoing behavior or in a lack of cognitive flexibility. If the organism is not able to maintain the ongoing goal-oriented behavior with a certain level of stress, or if the organism shifts to habitual (or reflexive) responses, even with a minor increase of the stress levels, this would suggest a failure in inhibitory control.

In this perspective, traditional executive components (i.e., updating, monitoring, problem solving, cognitive flexibility, and control inhibition) could not be accessed without taking into account their role in the entire adaptive process and the optimization of cognitive effort due to a perceived stress. In this sense, different from the majority of traditional multi-component models of executive functions that emphasized high-order quality of the cognitive processes, or the majority of dual-processing models that expanded the traditional models investigating the "mirrored" features (**Figures 1B,C**), the dynamic executive functioning hypothesis – based upon the salience and executive control neuronal networks proposed by Hermans et al. (2014) – intended to set aside these conceptual categorical borders commonly used to define executive behaviors, suggesting that an optimal adaptive process would consider the constant interaction between an emotional salience axis and executive controlled axis.

As shown in **Figure 1**, executive functioning would: (1) constantly monitor the environment, adjusting the ongoing behavior as soon as new demands are identified; and (2) promote the automation of successful behavioral strategies. The first point is in accordance with the first assumption presented in the beginning of this section. Considering that executive functioning is an adaptive process, it means that without any environmental demand the organism remain in a homeostatic state, for example the so-called Default Mode Network that usually is found when neuroimaging studies investigate participants at rest (Damoiseaux et al., 2006). However, even without a demand capable of triggering goal-oriented behaviors, people still need to monitor and perceive environmental changes, which is likely supported by the synchronicity found between the brain salience network and default mode network at rest, whose disruption falls over dysfunctional thinking (Orliac et al., 2013). The second point means that as soon as a new goal-oriented behavior achieves success in responding to environmental demand, it should be added to the repertoire of successful behavioral strategies of the organisms. This point refers directly to the second assumption also presented in the beginning of this section, which claims that executive functioning should be comprehended as a continuous adaptive process that enables the organism to save cognitive resources when faced with the same environmental demand. This aspect has a key evolutionary purpose since the organism would be able to retrieve previous information to solve similar environmental demands without allocating additional efforts to learn completely new strategies. Even though automaticity has been largely discussed and still lacks consensus, most views of automaticity share the assumption that training and repetition may lead to changes in effort and cognitive demands (Moors and De Houwer, 2006).

Furthermore, executive functioning could be exemplified in daily life situations, particularly, since when we face a new environmental demand (an important appointment or any unpredictable event) cognitive resources should be allocated to cope with that event. Indeed, even relatively low-level cognitive processes can be regulated through environmental stimulus, such as priming. Some authors have suggested that selective attention could be comprehended as a strategic self-regulatory process, since it allows that individuals focus their attention on the goal-relevant information (Fitzsimons and Bargh, 2004). Thus, it seems to be counterintuitive to think that an individual can be emotionally engaged with a certain task while no cognitive resources are allocated to cope with it, at least, on some basic attentional level.

To give another example of our executive functioning hypothesis, we propose a re-interpretation of the most popular example of prefrontal lobe lesion and executive dysfunction, Phineas Gage. The case was first published by Harlow (1868) and since then has inspired the executive functions research and modern hypotheses, such as the somatic marker (Damasio, 1995). Not surprisingly, great attention is given to the fact that the reliable and hardworking foreman miraculously survived after a serious accident in which a tamping iron went through his frontal lobe. Even more surprisingly is that approximately 3 months after the accident, Gage was recovered enough to travel and meet his family. However, in a later report, Harlow (1868) described that previous to his injury Gage "was looked upon by those who knew him as a shrewd, smart business man, very energetic and persistent in executing all his plans of operation," but afterward he was "no longer Gage." Although many executive functions models have focused on this point, to illustrate our hypothesis we briefly highlight a peculiar moment that may have happened few minutes before the accident.

According to some reports, Gage's task consisted of adding blasting powder and a fuse in a hole drilled into the rock, then using the tamping iron to pack sand into the hole above the powder. After "the powder and fuse had been adjusted in the hole, and he was in the act of 'tamping it in,' his attention was attracted by his men in the pit behind him" (. . .) "at the same instant dropping the iron upon the charge, it struck fire upon the rock, and the explosion followed" (Harlow, 1868). Within our perspective, the failure in maintaining the primary attentional focus on the task could also be described as an executive functioning failure. After a couple of months of performing the same tasks and procedures, it is possible that the individual became used to it, automating some behaviors. In the meantime, the emotional salience associated with the dangerousness of the task also decreased and the likelihood to commit a mistake gradually increased. In other words, it is possible that Gage was

working in an automatic-resting state and was not able to update the new environmental demand in time. The same would have occurred with any individual working on an assembly line, or any other activity that requires repeating a series of procedures during a certain period.

On the contrary, during a lecture, teachers should be cognitively engaged to maintain the attentional focus on the topic, while delivering an informative but attractive speech. Their work require highly specialized knowledge and abilities; integrating a series of cognitive processes, such as perception, attention, memory, theory of mind, etc. The teachers in this example would be able to easily maintain low levels of stress and we could argue that they behave in a resting-control state, which is enough to keep them alert but not hypervigilant. The resting-control state is responsible for the majority of goal-oriented behaviors, and it is commonly described as the high-order cognitive abilities associated with traditional multi-component models of executive functions. Continuing with this example, after a 3-h lecture some arrogant students become bored, making noise and telling jokes. The teacher easily becomes stressed, but he/she maintains the same level of his/her lecture, while thinking about the available options to solve this annoyance. The teacher behaves in an "emotional salient-control" state, in which maintaining the executive functioning is extensively exhausting. After asking for respect and silence more than once, a laugh is heard and the teacher immediately yells at students to leave the class. The executive functioning was not enough to inhibit the response and for that reason it could illustrate an "emotional salient-automatic" behavior that solved the problem, but makes the teacher embarrassed. Without the arrogant and noisy students, the teacher relaxes and the lecture continues, now in a resting-automatic state. Although **Figure 1** suggests an adaptive process in which the organism goes through the same states, but in a specific direction (i.e., H, a, b, c), this example also shows that the executive functioning is constantly regulating the allocation of cognitive resources and emotional salience. The next time that the teacher faces a similar situation, he/she could utilize gist representations of the previous event, taking effective split-second decisions without reaching the peak of stress.

The theoretical hypothesis of executive functioning is not intended to go against any specific model or theory, but compile some important features already observed and deeply discussed by other models. Therefore, our goal is to integrate these features to suggest a more comprehensive executive functioning hypothesis, focusing on a continuous adaptive process. The similarities between different models of executive functions are evident when considering the key issues that these models seek to explain: How automatic responses are suppressed in favor of controlled responses? Are controlled responses effortful? If yes, in which way? How working memory capacity influences the suppression of automatic responses and the variability of controlled responses? What are the roles of executive functions in emotional, behavioral, and cognitive self-regulation? Considering these, some comparisons with previous models and theories could help to elucidate some features of our executive functioning perspective.

In this sense, Teuber (1972) was one of the first researchers to synthesize and discuss evidences that the PFC could anticipate consequences based upon sensory systems information, elucidating that emotional responses could be necessary to adequate cognitive functioning in some circumstances. His studies proposed an executive functions framework with a twofold gradient, including a vertical up–down gradient (related to emotional reactivity) and a horizontal back-to-front gradient (related to delay-response task) that modulates sensory systems in anticipation of future changes (Teuber, 1972). The two-fold gradient model from Teuber greatly influenced many future works, as well as the present hypothesis, because it emphasized that a certain level of emotional responses should be important to goal-oriented behaviors. Further studies from Fuster (2006), Stuss and Levine (2002), and Zelazo and Carlson (2012), for example, investigated the energizing effect of emotions in cognition and the self-regulatory aspects of executive functions.

Another important issue of our executive functioning hypothesis refers to the adaptive capacity of the organism to retrieve previous successful strategies. This idea was mostly based upon the model from Norman and Shallice (1983), which postulated that automatic responses should be suppressed in favor of more assertive ones. Initially, the idea of an automatic-controlled axis corroborates with the notion of an attentional control – described by Norman and Shallice (1983) as SAS – that emerged when routine schemas become unable to deal with non-routine circumstances. The major contribution of SAS to our perspective is based upon the idea that our attention could operate in different well-defined levels. Moreover, in accordance with the authors, the SAS indicates that individuals applied previously learned strategies to novel problems, highlighting that an executive functioning may be critical for adaptive behavior and the improvement of cognitive schemes for problem resolutions, as we discussed. By this token, it also has similarities with the theoretical and conceptual analysis of automaticity proposed by Moors and De Houwer (2006) by assuming that practice can lead to less effort in processing – something that some call automaticity – and that cognitive functioning works in a gradual manner. However, this model assumes that this dynamic process works through different features involved in automatic and controlled processes separately, and that the combination of some of these features that may influence types of behaviors/processes that we often call automatic, should in fact be considered an umbrella term for a range of features.

Interestingly, the capacity to improve previous cognitive schemes may be related to the capacity of self-monitoring and behavior inhibition since individuals might be able to anticipate future outcomes according with their own behavior (Barkley, 2001). Barkley (2001) also suggests that an executive functions model may take into account an evolutionary principle of gradualism. Therefore, executive functions may be understood as a continuum form of mental capacity that might be observed in other species, in which human beings show the higher capacity of mental representation concerning future perspectives and the ability to inhibit undesirable behaviors (Barkley, 2001). In this sense, the capacity to constantly update environmental contingencies and inhibit behaviors also seems to be a central

aspect in our perspective since it allows the individual to transit by all behavioral states (**Figure 1**), predicting hypothetical futures based upon previous experiences and them inhibiting an automatic response in favor of a controlled one (SAS influence).

More recently, Asp et al. (2013) defined this monitoring/updating characteristic of inhibitory control as the False Tag Theory (FTT), suggesting that affective processes signalize inappropriate responses ("false tags"). In order to include affective processing, the authors also suggest that the capacity to "false tag" inappropriate responses has a limited resource, which can be taxed during periods of high cognitive work (Asp et al., 2013). In this sense, the FTT extended the Somatic Marker Theory (SMT) proposed by Damasio (1996), which elucidated that decision-making is an emotion-dependent process that is wrought through the repetition of experiences. However, FTT proposes how affective signaling could operate with cognitive processes, showing that if there is a concurrent requirement of both "false tagging" to perceptual and cognitive representations, there can be competition for the "false tagging" resource and the efficacy of each process may be decreased (Asp et al., 2013). For our perspective, it corroborates with the idea that cognitive processes are influenced by emotional salience, facilitating or biasing cognitive processes.

Finally, our executive functioning hypothesis is in accordance with the Hot-Cold Decision Triangle (Yang et al., 2012) and the Tri-dimensional Processing model (Varga and Hamburger, 2014). First, both models emerged as a criticism of standard dual-processing models, each one focusing on different arguments. Yang et al. (2012) discuss that effortlessly and effortful cognitive engagement are mediated by an emotional processing, the model suggests that optimal and healthier decisions are influenced by the extent to which System 1 overlaps System 2. Our perspective of executive functioning is different from the Hot-Cold Decision Triangle because their model assumes a prescriptive framework in which optimal decisions are made with less emotional engagement. Moreover, the Tri-dimensional Processing model also added an important issue concerning the continuous dimensions of information processing. However, the authors did not suggest it as an executive functioning outcome, derived from the interaction between automatic-controlled behaviors and emotional salience. This interaction was deeply discussed by Ernst (2014), who suggested that the efficient adaptive behavior would result from the balance between appetitive (striatum-dependent) and avoidant (amygdala-dependent) processes. In his model, PFC works as a "conductor" and regulates approach-avoidant behaviors according to environmental demands (Ernst, 2014).

FUTURE PERSPECTIVES

Instead of presenting a new model, the executive functioning hypothesis presented here should question the current hierarchical and categorical framework and be interpreted as an alternative perspective for future studies. An executive functioning perspective may favor novel discussions about which individual factors can mediate the balance between emotional salience and automatic-controlled behaviors. For example, the threshold of the amount of stress that someone could tolerate to maintain goal-oriented behaviors (emotional salient-controlled state) and not act impulsively (emotional salient-automatic state), may be influenced by personality traits and early experiences, as well as developmental stages and genetic background. Specifically, positive and negative urgency are individual characteristics that are marked by the ineffective control of decisions under extreme emotional states, and particularly, people react differently under different emotional states (Cyders and Smith, 2008). There are some individuals who react rashly to emotional states with positive valences (which means they present positive urgency), and there are people who can react rashly only under negative emotional states (which means they present negative urgency). It has been documented that a combination of personality factors contributes to positive and negative urgency (Gay et al., 2008). With regards to genetic factors, there are evidences suggesting that polymorphisms in the dopamine receptors and serotonin transporters genes are related to positive and negative urgency related to decision-making [for a review about positive and negative urgency and those consequences for behavior, see (Billieux et al., 2010).

Moreover, as reviewed by Peterson and Welsh (2014), an additional feature that should be clearly elucidated concerns the emotional-salience axis. Although dual-processing models theoretically assume that "cold" and "hot" are not independent features of executive functions, in practice the "thermal gradient" between them is still poorly understood. Future researches in experimental psychological should manipulate the "temperature" of a single task (Peterson and Welsh, 2014). Using an interesting approach combining behavioral economic and computational modeling, Summerfield et al. (2011) investigated the allocation of higher-order cognitive strategies by manipulating the volatility of the environment (i.e., the level of uncertainty when environment can change rapidly and without warning). On the other hand, a computational working memory model seems to fit the individual's behavior better during high-volatile (i.e., uncertainty) scenarios. Interesting, the authors suggested that the optimal (Bayesian) decision model predicted-related activity in more posterior regions of the medial PFC while anterior regions of the medial PFC actively respond when decisions are based on motivational information (Summerfield et al., 2011). Likewise, our recent work suggested that during scenarios in which participants have no knowledge about their own performance and lower emotional arousal responses (for more details see Huang et al., 2013), their behavior is mostly modulated by the use of the available information in the decision scenario. Conversely, if some feedback is provided, participants tend to use less or even no available information about the environmental risks (Kluwe-Schiavon et al., 2016). These data are in line with the idea that contingency learning, habitual behavior, and goal-directed behavior could be studied as a continuum modulated by the uncertainty of the environment. Furthermore, manipulating these variables – environmental volatility or the presence of feedback – in experimental contexts might be an effective way to understand behavioral and neural mechanisms behind updating previously learned schemas. Bearing in mind that our

model considers an executive functioning that updates itself continuously, integrating both external and internal homeostatic changes, stress paradigms, such as the Trier Social Stress Test (TSST), seem to be a promising option. In this sense, it should be noted that a recent study showed that stressful situations mimicked by the TSST, elicited a stronger activation of the PFC associated with a risky decision-making process (Gathmann et al., 2014).

Additionally, one could question how our executive functioning hypothesis would account for dissociation between different components of executive functions that can be observed in health and mental illness (e.g., how would this hypothesis account for impaired reasoning and problem solving but intact working memory, or impaired working memory but intact inhibitory control). As supported by Summerfield et al. (2011), a dimensional perspective of executive functioning would be able to identify the amount of environmental volatility that someone may confront until goal-oriented responses shift to habitual responses. In this sense, it is still possible that someone could have an intact working memory and impaired problem solving, especially because according to our hypothesis, good performance in working memory could favor the individual to respond to the environmental demand based upon ongoing feedback, without necessarily allocating excessive cognitive resources to planning and problem solving. The same could occur with someone who has an impaired working memory but intact inhibitory control. In this case, someone that presents a decrease in working memory capacity (meaning that less information is retained in his/her memory span) could also present high behavioral variability, which is different from impulsivity or impairments in inhibitory control. It is possible that the same person would not have problems in inhibiting an automatic response when a high emotional-salient stimulus is shown. However, it is true that according to our hypothesis, it would be harder to explain someone who has an impaired working memory but has no difficulties in successfully planning goal-oriented behaviors. This point is important, once more, to illustrate that the current categorical multi-component view of executive functions is still focused on classifying which behaviors should represent cognitive flexibility or inhibitory control (Diamond, 2013), instead of understanding each behavior as a reflex of an adaptive process.

Finally, when we propose different axis we are not assuming consistently that there is a marked frontier between each axis, but we perform an estimation that is relative for understanding proposes. This criteria is similar to that suggested by Moors and De Houwer (2006) when they flagged one limitation of theories that use gradual models. In this sense, further studies could be done to clearly define emotional-salience states and automatic-controlled responses in order to measure it accurately. Based upon a behavioral perspective, it is possible to infer that automatic responses could be defined as those reflexive or conditioned responses. We hypothesized that automatic responses are more likely to occur in an environment with a very high or very low emotional-salience. Moors and De Houwer (2006) discussed that we can identify automaticity by viewing components/features that probably play a more significant role in less controlled processes (e.g., unconscious, unintentionally, or autonomous processing). This view indicated the need to use decompositional methods to investigate automaticity and highlighted that some combinations of different features can give us insight into the dynamics of cognitive control (Moors and De Houwer, 2006). On the other side of the automatic-controlled axis, controlled responses could be defined as those goal-oriented, non-conditioned responses that according to our hypothesis, are more likely to occur with middle-level emotional-salience. However, a clear definition of emotional-salience state is needed. For example, as discussed by Shields et al. (2016) and extensively described by McEwen et al. (2015), the effects of stress on executive functions goes beyond cortisol alone and the HPA-axis, since circulating proinflammatory cytokines can also have an impact on working memory (Marsland et al., 2006) and cognitive flexibility (Levandowski et al., 2016). Further studies should investigate multiple hormones and immune system processes in order to deeply understand the biological mechanisms behind the effects of stress on executive functions (Shields et al., 2016).

AUTHOR CONTRIBUTIONS

BK-S substantially contributed to the conception of the model and design of the work; AND, drafting the work and revising it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately discussed and resolved. TWV contributed to drafting the work and revising it critically for important intellectual content; AND final approval of the version to be published. BS-V substantially contributed to the conception of the model and design of the work; AND drafting the work. LM-D final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately discussed and resolved. RG-O substantially contributed to the conception of the model and design of the work, AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately discussed and resolved.

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REFERENCES

Anticevic, A., Dowd, E. C., and Barch, D. M. (2013). "Cognitive and motivational neuroscience of psychotic disorders," in *Neurobiology of Mental Illness*, 4 Edn, eds D. S. Charney, J. D. Buxbaum, P. Sklar, and E. J. Nestler (New York, NY: Oxford University Press), 269–286.

Ardila, A. (2008). On the evolutionary origins of executive functions. *Brain Cogn.* 68, 92–99. doi: 10.1016/j.bandc.2008.03.003

Aron, A. R. (2011). From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. *Biol. Psychiatry* 69, e55–e68. doi: 10.1016/j.biopsych.2010.07.024

Asp, E., Manzel, K., Koestner, B., Denburg, N., and Tranel, D. (2013). Benefit of the doubt: a new view of the role of the prefrontal cortex in executive functioning and decision making. *Front. Neurosci.* 7:86. doi: 10.3389/fnins.2013.00086

Atkinson, R. C., and Shiffrin, R. M. (1971). The control of short-term memory. *Sci. Am.* 225, 82–90. doi: 10.1038/scientificamerican0871-82

Baddeley, A. (2012). Working memory: theories, models, and controversies. *Annu. Rev. Psychol.* 63, 1–29. doi: 10.1146/annurev-psych-120710-100422

Barch, D. M., and Ceaser, A. (2012). Cognition in schizophrenia: core psychological and neural mechanisms. *Trends Cogn. Sci.* 16, 27–34. doi: 10.1016/j.tics.2011.11.015

Bargh, J. A. (1992). The ecology of automaticity: toward establishing the conditions needed to produce automatic processing effects. *Am. J. Psychol.* 105, 181–199. doi: 10.2307/1423027

Barkley, R. A. (2001). The executive functions and self-regulation: an evolutionary neuropsychological perspective. *Neuropsychol. Rev.* 11, 1–29. doi: 10.1023/A:1009085417776

Barkley, R. A. (2012). *Executive Functions: What They Are, How They Work, and why they Evolved*. London: The Guilford Press.

Bar-On, R., Tranel, D., Denburg, N. L., and Bechara, A. (2003). Exploring the neurological substrate of emotional and social intelligence. *Brain* 126, 1790–1800. doi: 10.1093/brain/awg177

Barsegyan, A., Mackenzie, S. M., Kurose, B. D., Mcgaugh, J. L., and Roozendaal, B. (2010). Glucocorticoids in the prefrontal cortex enhance memory consolidation and impair working memory by a common neural mechanism. *Proc. Natl. Acad. Sci. U.S.A.* 107, 16655–16660. doi: 10.1073/pnas.1011975107

Benningfield, M. M., Blackford, J. U., Ellsworth, M. E., Samanez-Larkin, G. R., Martin, P. R., Cowan, R. L., et al. (2014). Caudate responses to reward anticipation associated with delay discounting behavior in healthy youth. *Dev. Cogn. Neurosci.* 7, 43–52. doi: 10.1016/j.dcn.2013.10.009

Billieux, J., Gay, P., Rochat, L., and Van Der Linden, M. (2010). The role of urgency and its underlying psychological mechanisms in problematic behaviours. *Behav. Res. Ther.* 48, 1085–1096. doi: 10.1016/j.brat.2010.07.008

Collette, F., Van Der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., et al. (2005). Exploring the unity and diversity of the neural substrates of executive functioning. *Hum. Brain Mapp.* 25, 409–423. doi: 10.1002/hbm.20118

Cyders, M. A., and Smith, G. T. (2008). Emotion-based dispositions to rash action: positive and negative urgency. *Psychol. Bull.* 134, 807–828. doi: 10.1037/a0013341

Damasio, A. R. (1995). *Descarte's Error: Emotion, Reason and the Human Brain*. New York, NY: G.P. Putnam.

Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos. Trans. R. Soc. B Biol. Sci.* 351, 1413–1420. doi: 10.1098/rstb.1996.0125

Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., et al. (2006). Consistent resting-state networks across healthy subjects. *Proc. Natl. Acad. Sci. U.S.A.* 103, 13848–13853. doi: 10.1073/pnas.0601417103

Diamond, A. (2013). Executive Functions. *Annu. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

Dunn, B. D., Dalgleish, T., and Lawrence, A. D. (2006). The somatic marker hypothesis: a critical evaluation. *Neurosci. Biobehav. Rev.* 30, 239–271. doi: 10.1016/j.neubiorev.2005.07.001

Emcdda. (2014). *European Monitoring Centre for Drugs and Drug Addiction: European Drug Report: Trends and Developments*. Luxemburgo: Publications Office of the European Union.

Ernst, M. (2014). The triadic model perspective for the study of adolescent motivated behavior. *Brain Cogn.* 89, 104–111. doi: 10.1016/j.bandc.2014.01.006

Evans, J. S. B. T. (2008). Dual-processing accounts of reasoning, judgment, and social cognition. *Annu. Rev. Psychol.* 59, 255–278. doi: 10.1146/annurev.psych.59.103006.093629

Fitzsimons, G. M., and Bargh, J. A. (2004). "Automatic self-regulation," in *Handbook of Self-Regulation: Research, Theory, and Applications*, eds R. F. Baumeister and K. D. Vohs (London: The Guilford Press).

Fuster, J. M. (2006). The cognit: a network model of cortical representation. *Int. J. Psychophysiol.* 60, 125–132. doi: 10.1016/j.ijpsycho.2005.12.015

Gathmann, B., Schulte, F. P., Maderwald, S., Pawlikowski, M., Starcke, K., Schäfer, L. C., et al. (2014). Stress and decision making: neural correlates of the interaction between stress, executive functions, and decision making under risk. *Exp. Brain Res.* 232, 957–973. doi: 10.1007/s00221-013-3808-6

Gay, P., Rochat, L., Billieux, J., D'acremont, M., and Van Der Linden, M. (2008). Heterogeneous inhibition processes involved in different facets of self-reported impulsivity: evidence from a community sample. *Acta Psychol.* 129, 332–339. doi: 10.1016/j.actpsy.2008.08.010

Gladwin, T. E., and Figner, B. (2014). ""Hot" cognition and dual systems: introduction, criticisms, and ways forward," in *Frontiers of Cognitive Psychology Series: Neuroeconomics, Judgment and Decision Making*, eds E. A. Wilhelms and V. F. Reyna (London: Psychology Press), 157–181.

Gladwin, T. E., Figner, B., Crone, E. A., and Wiers, R. W. (2011). Addiction, adolescence, and the integration of control and motivation. *Dev. Cogn. Neurosci.* 1, 364–376. doi: 10.1016/j.dcn.2011.06.008

Goldstein, S., Naglieri, J., Princiotta, D., and Otero, T. (2014). "Introduction: a history of executive functioning as a theoretical and clinical construct," in *Handbook of Executive Functioning*, eds S. Goldstein and J. Naglieri (New York, NY: Springer), 3–12.

Harlow, J. (1868). Recovery from the passage of an iron bar throught the head. *Publications Massachusetts Med. Soc.* 2, 327–347.

Hermans, E. J., Henckens, M. J., Joels, M., and Fernandez, G. (2014). Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends Neurosci.* 37, 304–314. doi: 10.1016/j.tins.2014.03.006

Huang, Y., Wood, S., Berger, D. E., and Hanoch, Y. (2013). Risky choice in younger versus older adults: affective context matters. *Judgm. Decis. Mak.* 8, 179–187.

Jurado, M. B., and Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychol. Rev.* 17, 213–233. doi: 10.1007/s11065-007-9040-z

Kahneman, D. (2011). *Thinking, Fast and Slow*. New York, NY: Farrar, Straus and Giroux.

Kahneman, D., and Tversky, A. (2000). *Choices, Values, and Frames*. Cambridge: Cambridge University Press.

Kluwe-Schiavon, B., Sanvicente-Vieira, B., Kristensen, C. H., and Grassi-Oliveira, R. (2013). Executive functions rehabilitation for schizophrenia: a critical systematic review. *J. Psychiatr. Res.* 47, 91–104. doi: 10.1016/j.jpsychires.2012.10.001

Kluwe-Schiavon, B., Viola, T. W., and Grassi-Oliveira, R. (2012). Modelos teóricos sobre construto único ou múltiplos processos das funções executivas. *Rev. Neuropsicol. Latinoamericana* 4, 29–34.

Kluwe-Schiavon, B., Viola, T. W., Sanvicente-Vieira, B., Pezzi, J. C., and Grassi-Oliveira, R. (2016). Similarities between adult female crack cocaine users and adolescents in risky decision-making scenarios. *J. Clin. Exp. Neuropsychol.* 38, 795–810. doi: 10.1080/13803395.2016.1167171

Leh, S. E., Petrides, M., and Strafella, A. P. (2010). The neural circuitry of executive functions in healthy subjects and Parkinson's disease. *Neuropsychopharmacology* 35, 70–85. doi: 10.1038/npp.2009.88

Levandowski, M. L., Hess, A. R., Grassi-Oliveira, R., and De Almeida, R. M. (2016). Plasma interleukin-6 and executive function in crack cocaine-dependent women. *Neurosci. Lett.* 628, 85–90. doi: 10.1016/j.neulet.2016.06.023

Lezak, M. D. (1982). The problem of assessing executive functions. *Int. J. Psychol.* 17, 281–297. doi: 10.1080/00207598208247445

Lezak, M. D. (1995). *Neurpsychological Assessment*. New York, NY: Oxford University Press.

Lezak, M. D., Howieson, D. B., Bigler, E. D., and Tranel, D. (2012). *Neuropsychological Assessment*. New York, NY: Oxford University Press.

Li, X., Lu, Z. L., D'argembeau, A., Ng, M., and Bechara, A. (2010). The iowa gambling task in fMRI images. *Hum. Brain Mapp.* 31, 410–423. doi: 10.1002/hbm.20875

Liu, K. C., Chan, R. C., Chan, K. K., Tang, J. Y., Chiu, C. P., Lam, M. M., et al. (2011). Executive function in first-episode schizophrenia: a three-year longitudinal study of an ecologically valid test. *Schizophr. Res.* 126, 87–92. doi: 10.1016/j.schres.2010.11.023

Luria, A. R. (1970). Functional organization of brain. *Sci. Am.* 222, 66–72. doi: 10.1038/scientificamerican0370-66

Marsland, A. L., Petersen, K. L., Sathanoori, R., Muldoon, M. F., Neumann, S. A., Ryan, C., et al. (2006). Interleukin-6 covaries inversely with cognitive performance among middle-aged community volunteers. *Psychosom. Med.* 68, 895–903. doi: 10.1097/01.psy.0000238451.22174.92

McEwen, B. S., Gray, J., and Nasca, C. (2015). Recognizing resilience: learning from the effects of stress on the brain. *Neurobiol. Stress* 1, 1–11. doi: 10.1016/j.ynstr.2014.09.001

McKlveen, J. M., Myers, B., and Herman, J. P. (2015). The medial prefrontal cortex: coordinator of autonomic, neuroendocrine and behavioural responses to stress. *J. Neuroendocrinol.* 27, 446–456. doi: 10.1111/jne.12272

Miller, G. A. (2003). The cognitive revolution: a historical perspective. *Trends Cogn. Sci.* 7, 141–144. doi: 10.1016/S1364-6613(03)00029-9

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cognit. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Moors, A., and De Houwer, J. (2006). Automaticity: a theoretical and conceptual analysis. *Psychol. Bull.* 132, 297–326. doi: 10.1037/0033-2909.132.2.297

Morris, S. E., and Cuthbert, B. N. (2012). Research domain criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues Clin. Neurosci.* 14, 29–37.

Noël, X., Brevers, D., and Bechara, A. (2013). A triadic neurocognitive approach to addiction for clinical interventions. *Front. Psychiatry* 4:179. doi: 10.3389/fpsyt.2013.00179

Norman, D. A., and Shallice, T. (1983). Attention to action - willed and automatic-control of behavior. *Bull. Psychon. Soc.* 21, 354–354.

Orliac, F., Naveau, M., Joliot, M., Delcroix, N., Razafimandimby, A., Brazo, P., et al. (2013). Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. *Schizophr. Res.* 148, 74–80. doi: 10.1016/j.schres.2013.05.007

Peterson, E., and Welsh, M. (2014). "The development of hot and cool executive functions: are we getting warmer?," in *Handbook of Executive Functions*, eds S. Goldstein and J. A. Naglieri (New York, NY: Springer).

Posner, M. I., and Snyder, C. R. (2004). Attention and Cognitive Control. *Cogn. Psychol.* 205–223.

Posner, M. I., and Snyder, C. R. R. (1975). "Attention and cognitive control," in *Information Processing and Cognition: The Loyola Symposium*, ed. R. L. Solso (Hillsdale, NJ: Lawrence Erlbaum Associates), 55–85.

Pribram, K. H. (1973). "The primate frontal cortex-executive of the brain," in *Psychophysiology of the Frontal Lobes*, eds K. H. Pribram and A. R. Luria (New York, NY: Academic Press), 293–314.

Pripfl, J., Neumann, R., Köhler, U., and Lamm, C. (2013). Effects of transcranial direct current stimulation on risky decision making are mediated by 'hot' and 'cold' decisions, personality, and hemisphere. *Eur. J. Neurosci.* 38, 3778–3785. doi: 10.1111/ejn.12375

Reyna, V. F., and Brainerd, C. J. (2011). Dual processes in decision making and developmental neuroscience: a fuzzy-trace model. *Dev. Rev.* 31, 180–206.

Sahlin, N.-E., Wallin, A., and Persson, J. (2010). Decision science: from Ramsey to dual process theories. *Synthese* 172, 129–143. doi: 10.1007/s11229-009-9472-5

Shields, G. S., Bonner, J. C., and Moons, W. G. (2015). Does cortisol influence core executive functions? A meta-analysis of acute cortisol administration effects on working memory, inhibition, and set-shifting. *Psychoneuroendocrinology* 58, 91–103. doi: 10.1016/j.psyneuen.2015.04.017

Shields, G. S., Sazma, M. A., and Yonelinas, A. P. (2016). The effects of acute stress on core executive functions: a meta-analysis and comparison with cortisol. *Neurosci. Biobehav. Rev.* 68, 651–668. doi: 10.1016/j.neubiorev.2016.06.038

Starcke, K., and Brand, M. (2016). Effects of stress on decisions under uncertainty: a meta-analysis. *Psychol. Bull.* 142, 909–933. doi: 10.1037/bul0000060

Stuss, D. T. (2011). Traumatic brain injury: relation to executive dysfunction and the frontal lobes. *Curr. Opin. Neurol.* 24, 584–589. doi: 10.1097/WCO.0b013e32834c7eb9

Stuss, D. T., and Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu. Rev. Psychol.* 53, 401–433. doi: 10.1146/annurev.psych.53.100901.135220

Summerfield, C., Behrens, T. E., and Koechlin, E. (2011). Perceptual classification in a rapidly changing environment. *Neuron* 71, 725–736. doi: 10.1016/j.neuron.2011.06.022

Teuber, H. L. (1972). Unity and diversity of frontal lobe functions. *Acta Neurobiol. Exp.* 32, 615–65641.

Tirapu-Ustarroz, J., Garcia-Molina, A., Luna-Lario, P., Roig-Rovira, T., and Pelegrin-Valero, C. (2008a). Models of executive control and functions (I). *Rev. Neurol.* 46, 684–692.

Tirapu-Ustarroz, J., Garcia-Molina, A., Luna-Lario, P., Roig-Rovira, T., and Pelegrin-Valero, C. (2008b). Models of executive control and functions (II). *Rev. Neurol.* 46, 742–750.

Varga, A., and Hamburger, K. (2014). Beyond type 1 vs. type 2 processing: the tri-dimensional way. *Front. Psychol.* 5:993. doi: 10.3389/fpsyg.2014.00993

Volkow, N. D., and Baler, R. D. (2014). Addiction science: uncovering neurobiological complexity. *Neuropharmacology* 76(Pt B), 235–249. doi: 10.1016/j.neuropharm.2013.05.007

Yang, H., Carmon, Z., Kahn, B., Malani, A., Schwartz, J., Volpp, K., et al. (2012). The hot-cold decision triagle: a framework for healthier choices. *Mark. Lett.* 23, 457–472. doi: 10.1007/s11002-012-9179-0

Yuen, E. Y., Liu, W., Karatsoreos, I. N., Feng, J., Mcewen, B. S., and Yan, Z. (2009). Acute stress enhances glutamatergic transmission in prefrontal cortex and facilitates working memory. *Proc. Natl. Acad. Sci. U.S.A.* 106, 14075–14079. doi: 10.1073/pnas.0906791106

Zelazo, P. D., and Carlson, S. M. (2012). Hot and cool executive function in childhood and adolescence: development and plasticity. *Child Dev. Perspect.* 6, 354–360.

Zimmerman, D. L., Ownsworth, T., O'donovan, A., Roberts, J., and Gullo, M. J. (2016). Independence of hot and cold executive function deficits in high-functioning adults with autism spectrum disorder. *Front. Hum. Neurosci.* 10:24. doi: 10.3389/fnhum.2016.00024

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MINI REVIEW
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Unraveling Executive Functioning in Dual Diagnosis

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In mental health, the term dual-diagnosis is used for the co-occurrence of Substance Use Disorder (SUD) with another mental disorder. These co-occurring disorders can have a shared cause, and can cause/intensify each other's expression. Forming a threat to health and society, dual-diagnosis is associated with relapses in addiction-related behavior and a destructive lifestyle. This is due to a persistent failure to control impulses and the maintaining of inadequate self-regulatory behavior in daily life. Thus, several aspects of executive functioning like inhibitory, shifting and updating processes seem impaired in dual-diagnosis. Executive (dys-)function is currently even seen as a shared underlying key component of most mental disorders. However, the number of studies on diverse aspects of executive functioning in dual-diagnosis is limited. In the present review, a systematic overview of various aspects of executive functioning in dual-diagnosis is presented, striving for a prototypical profile of patients with dual-diagnosis. Looking at empirical results, inhibitory and shifting processes appear to be impaired for SUD combined with schizophrenia, bipolar disorder or cluster B personality disorders. Studies involving updating process tasks for dual-diagnosis were limited. More research that zooms in to the full diversity of these executive functions is needed in order to strengthen these findings. Detailed insight in the profile of strengths and weaknesses that underlies one's behavior and is related to diagnostic classifications, can lead to tailor-made assessment and indications for treatment, pointing out which aspects need attention and/or training in one's self-regulative abilities.

Keywords: executive functioning, dual-diagnosis, comorbidity, substance use disorder, alcohol use disorder, addiction, schizophrenia, bipolar

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INTRODUCTION

In dual-diagnosis, a Substance Use Disorder (SUD) co-occurs with another psychiatric condition such as psychotic disorder, mood disorder, anxiety disorder or personality disorder (Ziedonis and Brady, 2005). The Epidemiologic Catchment Area study, a comprehensive study of comorbidity, showed that the lifetime SUDs-rate in the general population was 17%, compared to 48% for persons with schizophrenia and 56% for persons with bipolar disorder (Regier et al., 1990). SUD is described in respectively 27 and 24% of patients with a depressive disorder or an anxiety disorder (Mueser et al., 2011; Dom et al., 2013). Studying a dual-diagnosis population is relevant,

because of the threat that SUD and dual-diagnosis form to health, society, and the presence of relapses in addiction-related behavior and destructive lifestyles (De Jong et al., 2006; World Health Organisation [WHO], 2011). In clinical practice dual-diagnosis frequently occurs whereas ideally distinguishable single disorder groups are rare. Disorders in dual-diagnosis can have a shared cause, or can cause/intensify each other's expression (Mueser et al., 1998). It is not always easy or possible to distinguish in which way the disorders causally interact or influence each other.

In most SUDs and other mental disorders self-regulatory behavior to manage daily life situations (involving work and relationships) falls short. Coping strategies are impaired, resulting in affective breakdowns (American Psychiatric Association, 2013). These frequently observed symptoms of psychiatric disorders point directly to deficits in executive functioning (EF) (among others: Barkley, 2001; Egger et al., 2007; Fernandez-Serrano et al., 2010; Wiers et al., 2012; Janssen, 2013; Luijten et al., 2013; Thoma and Daum, 2013; Goschke, 2014; Smith et al., 2014; Snyder et al., 2015). Executive (dis)-functioning is currently even seen as a shared underlying key component of most mental disorders (Egger et al., 2007; Janssen, 2013; Goschke, 2014; Snyder et al., 2015).

Executive functioning can be defined as all cognitive processes that regulate behavior in such a manner that it can be efficient and goal-orientated (Miyake et al., 2000; Barkley, 2001; Friedman et al., 2008; Miyake and Friedman, 2012; Snyder et al., 2015). Barkley (2001) describes EF as serving to "shift the control of behavior from the immediate context, social others, and the temporal now to self-regulation by internal representations regarding the hypothetical social future". Miyake et al. (2000) introduced a model of EF in which three key EF aspects were presented. Firstly, *Shifting* concerns the switch of attention between tasks/operations and/or mental sets. Translated into daily life, it involves mental flexibility to repeatedly let go of irrelevant and/or inappropriate behaviors (for example, drug use or attention bias to alcohol related cues) and switch to more adequate/relevant behaviors (like sporting or switch of television-channel). Secondly, *Updating* involves the process of actively manipulating and monitoring relevant information in working memory, in order to keep track of information that is old and needs actualization (Miyake et al., 2000). For SUD, it can involve craving. When longing for drugs, a patient may usually tend to call the drug dealer. But, in a recent relapse prevention session he or she learned about putting the numbers of supporting friends in their phone. As this is the first moment of intense craving after the session and intrusive substance-use thoughts already come to mind, the patient has to monitor his or her own behavior and promptly update these thoughts by thinking of the newly learned information and healthier thoughts. He or she needs to replace the old information about the drug dealer with the new information regarding their supportive friend's phone number. *Inhibition* is also needed in this scenario, and it is defined as the ability to inhibit dominant, automatic responses when necessary (Miyake et al., 2000; Barkley, 2001). *Inhibition is*, for instance, the suppression of approaching alcohol/drugs and/or calling the drug dealer. *Shifting, updating* and *inhibition* are all needed to some extent when making daily life decisions. For instance, when one wants to succeed in arriving at work on time tomorrow, thereby stopping destructive-avoidant behavior that was linked to one's SUD lifestyle: (i) *shifting* is needed to get up earlier than before and to repeatedly let go of attention biases triggering late night out fantasies, (ii) *inhibition* is needed to prevent this late night 'going out' with friends by stopping yourself from drinking/using and going home, (iii) *updating* is involved in checking an alternative work-route, thereby avoiding and replacing the old, coffee-shop route that would trigger craving. The interplay between EF aspects can influence self-regulation in daily life by reducing problem-behavior and raising more goal-directed behavior. In addition, EF can facilitate one's controlled coping with negative feelings and externalizing problem behaviors like substance-abuse/aggressive outbursts. On the contrary part, executive *dys*function can cause/aggravate negative feelings/behavioral outbursts by the perceived lack of control (Goschke, 2014).

The both unified and diverse aspects of EF can be placed in a model (Snyder et al., 2015, p. 13). EF can be assessed by global or more specific neurocognitive tasks (**Figure 1** for specific tasks). If severe executive dysfunctioning is expected, the use of both global and specific EF tasks is recommended by Snyder et al. (2015). *Inhibition* can be measured by Go–NoGo, Stop Signal, Approach Avoidance Tasks, the Stroop, Anti-saccade, Event Related Potential components like P300, self-report/rating measures such as the Frontal Systems Behavioral Scale, BIS-BAS scales (Behavioral Inhibition System-Behavioral Approach System) and by the MMPI-2 Impulse-Control index[1] (Stroop, 1935; Hallett, 1978; Butcher et al., 1989; Carver and White, 1994; Robbins et al., 1994; Roberts et al., 1994; Rogers and Monsell, 1995; Mayr and Kliegl, 2000; Grace and Malloy, 2001; Miyake et al., 2004; Handy, 2005; Franken et al., 2006; Friedman et al., 2008; Wiers et al., 2009; Wiers et al., 2010). *Shifting* can be measured by the Trail Making Test (Reitan, 1958), the Wisconsin Card Sorting Test (Berg, 1948), and other Category Switching Tasks. *Updating* can be measured by the letter memory task (Morris and Jones, 1990), keep track task (Yntema, 1963) or spatial n-back task.[1] *Updating* tasks involve monitoring of incoming information to check task-relevance, and replacement, update, of old non-relevant information by new information[1] (Snyder et al., 2015).

Impairments in EF aspects can trigger the appearance of mental disorders by several mechanisms such as (i) a failure to maintain goals when confronted with interfering desires that are difficult to *inhibit* and/or complicate *shifting* to more healthy goals, (ii) *inhibitory* impairment of impulsive responses, (iii) sticking attention to disorder-linked cues like substances that interfere with adequate *shifting*, (iv) impaired cognitive control (*inhibition*) and distorted anticipational planning, (v) reduced (emotional) stress regulation, and (vi) cognitive *in*flexibility (Goschke, 2014). These mechanisms negatively interfere with adequate impulse control and decision making, consequently also thwarting proper self-regulatory behavior in daily life.

Executive functioning impairments were described in several mental conditions like schizophrenia, bipolar-, anxiety-,

[1] Most of the tasks are described and categorized in a review by Snyder et al. (2015).

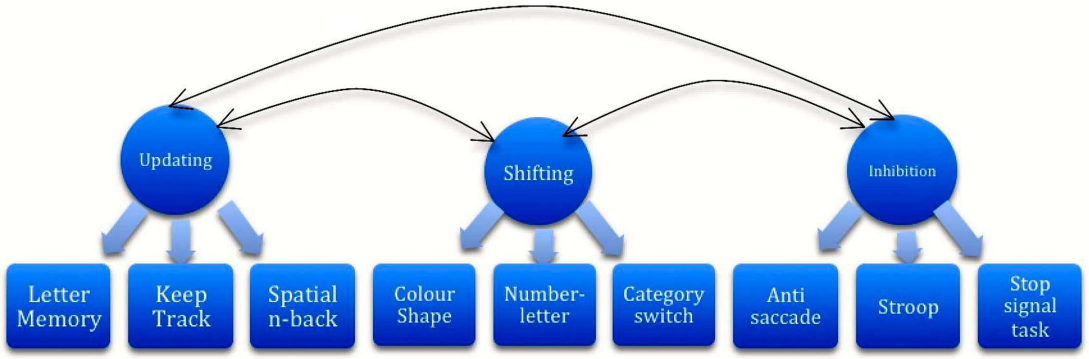

FIGURE 1 | Unified and diverse aspects of executive functioning (Snyder et al., 2015.)

personality-, developmental disorder, and SUD. For the separate disorders, a high number of studies have been undertaken and multiple reviews are present (see, among others, Verdejo-Garcia et al., 2006; Egger et al., 2007; Fernandez-Serrano et al., 2010; Wiers et al., 2012; Luijten et al., 2013; Thoma and Daum, 2013; Goschke, 2014; Smith et al., 2014; Snyder et al., 2015). Elaborating on this, one can expect that in dual-diagnosis EF will also be impaired. The majority of SUD-patients and half of schizophrenia/bipolar disorder patients are dually diagnosed. That makes insight into EF profiles for dual-diagnosis highly relevant, striving to unravel strengths and pitfalls for daily life behavior. For instance, the indications for treatment differ if one's pitfall primarily is the *inhibition* of undesired responses, or a flexible *shift* from one behavioral strategy to another. Recommendations for treatment can be formed when one oversees the differentiated profile of strengths and weaknesses, particularly in EF.

This article presents an overview of EF studies in dual-diagnosis.

MATERIALS AND METHODS

The inclusion criteria for studies were as follows: (i) A Method section that contains information concerning: (a) gender, age, test-materials and pre-assessment abstinence period of patients, and (b) diagnostic procedures that were used to determine if a dual-diagnosis was present or not; (ii) Comparisons by use of a healthy control group and/or a group without dual-diagnosis; and (iii) An abstinence period involving less risk for interfering influence of (sub-) acute substance effects, in order to only measure residual effects. The substance of study should not be traceable anymore. Studies with an abstinence period of at least one week were included. For cannabis, a period of four weeks was adhered to (for substance detection times see Verstraete, 2004; for interfering effects see Walvoort et al., 2013). Guidelines for PRISMA analysis were used to select papers (Moher et al., 2009). PRISMA analysis for Web of Science and PubMed resulted in 155 papers including the primary search terms of Executive Functioning AND dual-diagnosis. Four additional papers were found using other search term-combinations, and two additional papers were found by other sources such as on topic reviews (Rabin et al., 2011; Benaiges et al., 2010; Balanza-Martinez et al., 2015). Consequently, a total of 161 papers were screened (including duplicates). After screening, 131 papers were excluded for the following reasons: 121 papers involved the use of search terms in off-topic contexts: for instance, "dual" in "dual-task". Five studies concerned theoretical/qualitative research/reviews and five papers involved medical/different use of the dual-diagnosis term. 30 articles were assessed for eligibility. Of these, 19 were excluded after analysis, for the following reasons: 12 papers did not mention abstinence periods, two papers' method-sections did not contain gender/age/test materials, one paper was not found in full-text despite contacting authors and four papers were duplicates between searches. Finally, a total of 11 studies were selected based on the criteria (**Table 1**). Search terms were Executive Functioning, dual-diagnosis, Substance Use Disorder, alcohol use disorder, inhibition, updating, shifting, comorbidity, schizophrenia, bipolar disorder, personality disorder, anxiety disorder, mood disorder, developmental disorder, and addiction. The independent variable was the dual-diagnosis; the dependent variable was the level of functioning on EF tasks.

RESULTS

Findings are presented for 11 studies that involve the dual-diagnoses of SUD-Schizophrenia (six), SUD-Bipolar disorder (two), SUD-Personality disorders (two) and SUD-Conduct disorder (one). For SUD-Anxiety and SUD-Developmental disorder no studies were found. Results are organized by disorder, tasks and EF aspect. Significance levels and effect sizes are described if present (**Table 1**).

SUD-Schizophrenia

Rodriguez-Jiminez et al. (2010) performed the largest schizophrenia-SUD dual-diagnosis study, involving 82 patients with dual-diagnosis (Sch+) and 121 patients with Schizophrenia without SUD (Sch−). Results mostly showed comparable *Shifting* and EF general abilities for Sch+ and Sch−. The Sch+ group only functioned less at *Inhibitory* control as compared to the Sch− group. In two more studies, patients

TABLE 1 | Findings.

Dual-diagnosis	Authors	Tasks	*N*	Abstinence	Significant results
Schizophrenia and SUD	Benaiges et al., 2013	Trail Making Test (*Shifting*), Tower of Hanoi (*EF general*), Wisconsin Card Sorting Test (*Shifting, EF general*), Backwards digit subtest (*Working memory*), Iowa Gambling Task (*Decision Making*), Vocabulary (Other: premorbid verbal IQ)	30 DD 30 Schizophrenia without SUD 35 SUD	4 months	DD and SUD > Schizophrenia without SUD on: **Shifting* ($P < 0.05$, Effect Size 0.08) **Number of errors* ($P < 0.01$, Effect Size 0.13) *Speed ($P < 0.01$, Effect Size 0.10) SUD > Schizophrenia without SUD on: **Decision making* ($P < 0.05$, Effect Size 0.07)
Schizophrenia and SUD	Jockers-Scherübl et al., 2007	Trail Making Test (*Shifting*), Wisconsin Card Sorting Test (*Shifting, EF general*), Continuous Performance Test (Other), Wechsler Memory Scale (Other), WAIS-R subtests (Other)	19 DD 20 Schizophrenia without SUD 21 HC 18 SUD	28 days	#Premorbid IQ difference and education level (DD < SUD) (IQ $F = 7.88$, $P = 0.00$) #No Effect Sizes reported DD = Schizophrenia without SUD on: all measures (*Shifting, EF General*, Other) DD = SUD on: **Shifting* (Wisconsin Card Sorting Test) DD < SUD on: **Shifting* (Trail Making Test) ($F = 6.15$, $P = 0.02$) *WAIS Comprehension ($F = 18.71$, $P = 0.00$) Picture arrangement ($F = 4.45$, $P = 0.04$) Digit Symbol ($F = 4.66$, $P = 0.04$) *Verbal Memory($F = 11.29$, $P = 0.00$) *Attention (Symbols $F = 5.49$, $P = 0.03$; Digits $F = 6.80$, $P = 0.01$)

Schizophrenia and SUD	Rodriguez-Jiminez et al., 2010	Wisconsin Card Sorting Test (*Shifting, EF general*), Trail Making Test (*Shifting*), Stroop (*Inhibition*)	82 DD 121 Schizophrenia without SUD	1 month	#DD patients significantly younger age, more males and more psychotic episodes #No Effect Size reported #Age difference groups is factor of influence
					DD = Schizophrenia without SUD on: most executive measures (*Shifting, EF General*) DD < Schizophrenia without SUD on *Inhibition* task $P = 0.015$

Schizophrenia and SUD	Rodriguez-Jimenez et al., 2008	Wisconsin Card Sorting Test (*Shifting, EF general*)	65 DD 48 Schizophrenia without SUD	30 days	DD = Schizophrenia without SUD on: **Shifting* ($F = 0.382$, $P = 0.538$) **Perseverative Errors* ($F = 0.396$, $P = 0.530$)
Schizophrenia and SUD	Schnell et al., 2009	Trail Making test (*Shifting*), Verbal Fluency (*EF general*), Dual-Tasking (*EF*), Letter Number Span (*Working Memory*), Digit Symbol Test (Other), Auditory Verbal Learning and Memory Test (Other)	35 DD 34 Schizophrenia without SUD	3 weeks	DD > Schizophrenia without SUD on **Executive Function* **Working Memory* (Sum tasks $T = 2.923$, $P = 0.005$) (Max. span $T = 2.349$, $P = 0.022$) **Shifting* ($T = -2.590$, $P = 0.012$) *Verbal memory (Delayed recall $T = 2.263$, $P = 0.027$) (Recognition $T = 2.246$, $P = 0.028$) DD < Schizophrenia without SUD on academic achievement and vocabulary #Level of education in DD is lower than in Schizophrenia without SUD group #No Effect Sizes reported

(Continued)

TABLE 1 | Continued

Dual-diagnosis	Authors	Tasks	*N*	Abstinence	Significant results
Schizophrenia and SUD	Sevy et al., 2007	Trail Making Test (*Shifting*), Iowa Gambling Task (*Decision Making*), Controlled oral word association test (*EF*), CPT Identical Pairs test, Digit span subtest Wechsler Adult Intelligence Scale, California Verbal Learning test (all Other)	14 DD, 20 HC 13 Schizophrenia without SUD	1 week	#DD less education than Schizophrenia without SUD and HC group Schizophrenia (DD AND Schizophrenia without SUD) < HC on: **Shifting* ability *Other measured neurocognitive functions (NB: Not study topic!) DD and Schizophrenia without SUD = HC on: **Emotion-based decision-making* DD > Schizophrenia without SUD on: Digit span ($P < 0.048$)
Bipolar disorder and SUD	Marshall et al., 2012	Wisconsin Card Sorting Test (*Shifting, EF general*), Stroop (*Inhibition*), Parametric Go/No-Go task (*Inhibition*), FAS verbal fluency test (*EF*), Rey Complex Figure Test (*planning and other*), California verbal learning test-II, Purdue Pegboard test, Emotion Perception Test, Facial Emotion Perception Test, Digit Symbol Coding (all Other)	158 DD 97 HC 98 Bipolar without SUD	6 months	#Less education DD #No Effect Sizes reported DD < HC on: **Conceptual Reasoning and set-Shifting* (*Shifting*) ($F = 9.68$, $P = 0.001$) *Processing Speed and interference resolution (*Inhibition*) ($F = 15.88$, $P < 0.001$) **Inhibitory control* ($F = 5.50$, $P = 0.007$) *Visual Memory ($F = 8.84$, $P = 0.001$) *Fine Motor skill ($F = 10.32$, $P < 0.001$, DD < Bipolar without SUD on: **Shifting* ($P < 0.01$) *Visual memory ($P < 0.01$) *Conceptual reasoning ($P < 0.01$)
Bipolar disorder and SUD	Van Gorp et al., 1998	Wisconsin Card Sorting Test (*Shifting, EF general*), Stroop (*Inhibition*), Trail Making Test (*Shifting*), FAS verbal fluency test (*EF*), Rey Complex Figure Test (*Planning and other*) California verbal learning test (Other), National Adult Reading Test (Other)	12 DD 22 HC 13 Bipolar without SUD	6 months	#No Effect Sizes reported DD < HC on: **Shifting* (less finished categories on Wisconsin Card Sorting Test; $F = 4.2469$, $P = 0.02$) **Errors* Wisconsin Card Sorting Test ($F = 3.627$, $P = 0.04$) *Verbal memory ($F = 6.0427$, $P = 0.005$) Bipolar without SUD < HC on: *Verbal memory ($F = 6.0427$, $P = 0.005$) **Errors* Wisconsin Card Sorting Test ($F = 3.627$, $P = 0.04$)
Personality disorder and SUD	Albein-Urios et al., 2014	Letter-number sequencing (*Updating*), 2-back task (*Updating*), Delis-Kaplan Executive Function System Color Word Interference Test (*Inhibition and Shifting*), Category test (*Shifting*), D2 (Other)	37 DD 36 SUD 34 HC	>15 days	DD Cluster B PD < HC on: **Attention/Inhibition* ($F = 5.832$, $P < 0.001$, Effect Size 1.0) ($F = 2.866$, $P < 0.05$, Effect Size 0.7) ($F = 3.643$, $P < 0.05$, Effect Size 0.7) *Concentration ($F = 6.735$, $P < 0.001$, Effect Size 1.1) DD Cluster C PD < HC on: **Working memory* ($F = 5.591$, $P < 0.001$, Effect Size 1.1) **Updating* ($F = 4.021$, $P < 0.01$, Effect Size 1.1) *Concentration (no significance digit Effect Size 1.0) *Efficiency ($F = 5.433$, $P < 0.01$, Effect Size 1.0) SUD < HC on: **Shifting* ($F = 3.818$, $P < 0.05$, Effect Size 0.7) **Working memory* (no significance digit Effect Size 1.0) *Concentration (no significance digit Effect Size 0.9) *Efficiency (no significance digit Effect Size 0.8)

(Continued)

TABLE 1 | Continued

Dual-diagnosis	Authors	Tasks	N	Abstinence	Significant results
Personality disorder and SUD	Albein-Urios et al., 2013	Letter-number sequencing (*Updating*), 2-back task (*Updating*), Stroop (*Inhibition*), Category test (*Shifting*), D2 (Other)	32 DD 44 SUD 34 HC	>15 days	DD < HC on: **Shifting* ($F = 6.59$, $P = 0.002$, Effect Size 0.85) **Updating* ($F = 5.10$, $P = 0.008$, Effect Size 0.76) **Inhibition* ($F = 5.98$, $P = 0.003$, Effect Size 0.79) **Attention Total D2 score ($F = 10.85$, $P = 0.000$, Effect Size 1.01) Concentration D2 ($F = 14.60$, $P = 0.000$, Effect Size 1.24) Fluctuation D2 ($F = 12.27$, $P = 0.000$, Effect Size 1.05) DD < SUD on: **Attention (Effect Size 0.79, no significance digit) **Inhibition* (Effect Size 0.50, no significance digit)
Conduct disorder and SUD	Giancola and Mezzich, 2000	Porteus Maze Test (*Planning*), Vigilance Test (*Inhibition*), Motor restraint test (*Inhibition*), Stroop (*Inhibition*), Test Language Competence (Other), Peabody Individual Achievement Test-Revised (Other), WISC/WAIS-R (Other)	239 DD 63 SUD (+other disorders) 58 Conduct dis. without SUD 110 HC	2 weeks	#SUD and Conduct Disorder groups also have other psychiatric disorders, so not "only" disorders DD < HC on: **Inhibition* ($F = 5.48$, $P < 0.01$; $F = 4.55$, $P < 0.01$) **Planning* ($F = 4.41$, $P < 0.01$) **Intelligence, **Language **Academic Achievement

DD, Dual -diagnosis; HC, healthy controls; <functioning: worse level of functioning; >functioning: better functioning; SUD, Substance Use Disorder.

with Sch+ and patients with Sch− had similar results for several *shifting* tasks (Jockers-Scherübl et al., 2007; Rodriguez-Jimenez et al., 2008). Contradictory to those findings, two studies showed better functioning for patients with Sch+ as compared to Sch− on *shifting* abilities (Schnell et al., 2009; Benaiges et al., 2013). Furthermore, in one study, patients with Sch+ functioned less adequate at *shifting* (Trail Making Test) and *inhibition* tasks than patients with Sch− (Jockers-Scherübl et al., 2007). Lastly, Sevy et al., 2007; including a healthy control group) showed worse *shifting* abilities for Sch+ patients (schizophrenia-cannabis) as compared to healthy controls.

SUD-Bipolar Mood Disorder

Patients with SUD-bipolar disorder showed poorer functioning on mental *shifting* ability as compared to healthy controls, measured by the Wisconsin Card Sorting Test. That is, dual-diagnosis patients completed fewer categories than controls (Van Gorp et al., 1998). Marshall et al. (2012) described that patients with SUD-bipolar disorder had more executive (*inhibitory control, set-shifting,* and *interference resolution*) dysfunctions than controls and patients with bipolar disorder without SUD.

SUD-Personality Disorders

In 2013 and 2014, cocaine abusing patients with cluster B (borderline, narcissistic, histrionic, and anti-social) and cluster C (avoidant, dependent, and obsessive compulsive) personality disorders were studied at diverse EF. Patients with SUD-cluster B personality disorders, that is, more impulsive personality types, showed impairments in nearly all EF aspects as compared to controls and most specifically in *inhibitory control*. Patients with SUD-cluster C personality disorders, that is, more inhibited and obsessive personality types, showed more problems in *working memory* and *updating* ability. Patients with SUD as compared to the dual-diagnosis group had a better *inhibitory control*. However, compared to healthy controls, the SUD group also showed impairments in *shifting* and *working memory*. Patients with dual-diagnosis SUD-Personality disorders as a group consistently functioned less on *shifting, updating* and *inhibitory* abilities as compared to healthy controls (Albein-Urios et al., 2013; Albein-Urios et al., 2014).

SUD-Conduct Disorder

One study compared 239 females with dual-diagnosis to healthy controls. Impairments were shown for the dual-diagnosis group on *inhibition* and *planning* ability as compared to healthy controls (Giancola and Mezzich, 2000).

SUD-Anxiety Disorders, Developmental Disorders

Despite frequent co-occurrence of SUD-anxiety or SUD-developmental disorders (for prevalence numbers see Dom et al., 2013), we found no studies on EF for these groups.

DISCUSSION

Aim and Model

Aim and Model Gaining a prototypical profile of EF for dual-diagnosis. This is expected to contribute to tailor-made directions for treatment.

Findings

Findings Shifting and *inhibitory control* mostly are compromised in patients with dual-diagnosis as compared to healthy controls. If one were to think of dual-diagnosis and its overt behavioral symptoms, it is quite conceivable that dual-diagnosis implicates a high amount of (affective) turbulence and sensory sensitivity, since both substances and psychotic/bipolar/other symptoms have an interfering influence on the balance of several brain processes. Elaborating on this, maintaining a realistic view of daily life situations with flexible participation and properly timed inhibition when needed, is likely to be impaired. As compared to Sch−, patients with Sch+ show less *inhibitory control*. One possible explanation for this difference may be that patients with a SUD-combination show relatively more impulsivity, partly because the use of substances may negatively influence their dopaminergic *inhibitory* brain processes. Thereby, they seem to be less capable of inhibiting desires than patients without SUD. Furthermore, with a view to negative symptomatology, the schizophrenia patient-group is possibly more avoidant/*inhibited* than approaching in behavior manner. In terms of impulsivity, this hypothetical explanation also applies to the finding that patients with cluster B (impulsive type) personality disorder and SUD perform *inhibitory control* tasks less adequately than patients with only SUD. Whereas impulsive behavior has shown to negatively interfere with *inhibitory control*, it can also be influenced vice versa: common impulsive behavior in dual-diagnoses such as SUD-Bipolar disorder, SUD-cluster B Personality disorder and SUD-Conduct disorder (American Psychiatric Association, 2013) may be maintained or even urged by executive impairments. Impulsivity however seems to have a positive counterpart as well: the finding that Sch+ patients function slightly better on *shifting* abilities than Sch− patients may be linked to a higher tendency for impulsiveness and search for novelty in patients with SUD-combinations. This means that a flexible switch from familiar pathways to other routes may be easier for persons that are more impulsive and less rigid in behavior than for more avoidant persons that may seek and/or persevere in familiar styles of behavior.

Limitations Concerning Dual-Diagnosis Research

Some conflicting findings reduce the certainty with which conclusions can be stated. These contradictions may be partly caused by factors that influenced several studies, and that may have restricted the validity and reliability of the observed empirical findings in those studies. For instance, the study of Jockers-Scherübl et al. (2007), that of Schnell et al. (2009) and that of Sevy et al. (2007) involved differences in education levels between the Sch+ (lower education level) and Sch− group. Furthermore, in one study the Sch+ group included younger patients and involved more males than the Sch− group. The differences in age actually showed to be a factor in differences found between the groups; so the observed weakened inhibitory control may be affected by the younger age of the dual-diagnosis group (study of Rodriguez-Jiminez et al., 2010). Complications in dual-diagnosis research are possibly due to several reasons. Sample sizes are mostly modest because it is difficult to recruit patients that (i) are in a mild psychiatric state needed for sufficient testability, (ii) are motivated to cooperate and stop using substances, and (iii) have achieved substance-abstinence for a reasonable time prior to assessment, ideally confirmed by tests. A pre-assessment abstinence period of at least six weeks is best, in case of alcohol, but probably for other substances as well, due to the recovery that the body undergoes in this period of time (Weeda et al., 2006; Walvoort et al., 2013). The length of substance abstinence and methods are not always clearly documented, which reduces the validity and reliability of conclusions. Furthermore, when testing patients with dual-diagnosis, it is not clear which disorder and/or substance contributes to which specific empirical finding (Balanza-Martinez et al., 2015). Partly for that reason, disorders and substances are usually studied "separately". But procedures for dual-diagnosis presence are not always described. This makes it ambiguous whether separate disorders or dual-diagnosis is studied. For example, Giancola and Mezzich (2000) described a "SUD without dual-diagnosis" group in which no Conduct Disorder was present (2000); however, other psychiatric diagnoses were present in this "SUD" group, making it still a "dual-diagnosis" group.

Future Research

Findings lead to the following future research recommendations. Firstly, studying dual-diagnosis has value, when methods are described in a valid manner. Secondly, sufficiently long abstinence periods before assessment, preferably approximately 6 weeks, should be attained to prevent findings from being influenced by acute or sub-acute substance use effects (Weeda et al., 2006; Walvoort et al., 2013). Thirdly, the use of healthy control groups is highly recommended to enable valid comparisons. Fourthly, studies need to be performed in patient groups that also exist in clinical practice, such as dual-diagnosis involving anxiety and developmental disorders. Fifthly, research on all diverse aspects of EF is recommended, also involving Updating processes/working memory. Impairments in flexible shifting abilities, updating processes, or impairments in inhibitory control over undesired responses will most probably lead to different indications for treatment. Finally, findings as described should get more strength through follow up research, including the test of the stated impulsivity hypothesis. Elaborating on these recommendations, there are promising results regarding EF treatment interventions, for instance with Dys-executive Syndrome Treatment Programs and Approach-Avoidance/Inhibitory Intervention Training (among others, Boelen et al., 2012; Rinck et al., 2013; Sharbanee et al., 2014). Hence, unraveling EF in dual-diagnosis has great value for

coaching and treatment of patients, and it illustrates how the gap between neuroscience and psychotherapy can be bridged.

AUTHOR CONTRIBUTIONS

JD was first and corresponding author. She performed the literature search for this mini-review and wrote several concepts of the manuscript. She consulted CV on a regular basis as second author to revise concept manuscript versions and sharpen the described theoretical and empirical issues. CV revised concept versions and JE as last author was available for consultation during the project and revised the final concept version of the manuscript. In the end, the final manuscript and cover letter to be submitted was carefully revised by all three authors en JD eventually submitted the manuscript as first author.

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REFERENCES

Albein-Urios, N., Martinez-Gonzalez, J. M., Lozano, O., Moreno-Lopez, L., Soriano-Mas, C., and Verdejo-Garcia, A. (2013). Negative urgency, disinhibition and reduced temporal pole gray matter characterize the comorbidity of cocaine dependence and personality disorders. *Drug. Alcohol Depend.* 132, 131–137. doi: 10.1016/j.drugalcdep2013.02.008

Albein-Urios, N., Martinez-Gonzalez, J. M., Lozano-Royas, O., and Verdejo-Garcia, A. (2014). Executive functions in cocaine-dependent patients with cluster B and cluster C personality disorders. *Neuropsychology* 28, 84–90. doi: 10.1037/neu0000007

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*, 5th Edn. Arlington: American Psychiatric Association.

Balanza-Martinez, V., Crespo-Facorro, B., Gonzalez-Pinto, A., and Vieta, E. (2015). Bipolar disorder comorbid with alcohol use disorder: focus on neurocognitive correlates. *Front. Physiol.* 6:108. doi: 10.3389/fphys.2015.00108

Barkley, R. A. (2001). The executive functions and self-regulation: an evolutionary neuropsychological perspective. *Neuropsychol. Rev.* 11, 1–29. doi: 10.1023/A:1009085417776

Benaiges, I., Prat, G., and Adan, A. (2010). Neuropsychological aspects of dual diagnosis. *Curr. Drug Abuse Rev.* 3, 175–188. doi: 10.2174/1874473711003030175

Benaiges, I., Serra-Grabulosa, J. M., Prat, G., and Adan, A. (2013). Executive functioning in individuals with schizophrenia and/or cocaine dependence. *Hum. Psychopharmacol.* 28, 29–39. doi: 10.1002/hup.2279

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *J. Gen. Psychol.* 39, 15–22. doi: 10.1080/00221309.1948.9918159

Boelen, D., Spikman, J. M., Lamberts, K., Brouwer, W. H., and Fasotti, L. (2012). *Behandeling Van het Ddysexecutief Syndroom*. Amsterdam: Boom.

Butcher, J. N., Dahlstrom, W. G., Graham, J. R., Tellegen, A., and Kaemmer, B. (1989). *The Minnesota Multiphasic Personality Inventory-2 (MMPI-2): Manual for administration and scoring*. Minneapolis, MN: University of Minnesota Press.

Carver, C. S., and White, T. L. (1994). Behavioural inhibition, behavioural activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *J. Pers. Soc. Psychol.* 62, 319–333. doi: 10.1037/0022-3514.67.2.319

De Jong, C. A. J., Schellekens, A. F. A., Ellenbroek, B., Franke, B., and Verkes, R.-J. (2006). *The Course of Addiction: Neurobiological Predictors of Chronicity*. Cambridge, MA: Academic publications.

Dom, G., Dijkhuizen, A., van der Hoorn, B., Kroon, H., Muusse, C., van Rooijen, S., et al. (2013). *Handboek Dubbele Diagnose*. Utrecht: de Tijdstroom.

Egger, J. I. M., De Mey, H. R. A., and Janssen, G. T. L. (2007). Assessment of executive functioning in psychiatric disorders: functional diagnosis as the ouverture of treatment. *Clin. Neuropsychiatry* 4, 111–116.

Fernandez-Serrano, M. J., Perez-Garcia, M., Schmidt Rio-Valle, J., and Verdejo-Garcia, A. (2010). Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. *J. Psychopharmacol.* 24, 1317–1332. doi: 10.1177/0269881109349841

Franken, I. H. A., Muris, P., and Georgieva, I. (2006). Gray's model of personality and addiction. *Addict. Behav.* 31, 399–403. doi: 10.1016/j.addbeh.2005.05.022

Friedman, N. P., Miyake, A., Young, S. E., Defries, J. C., Corley, R. P., and Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Gen. J. Exp. Psychol.* 137, 201–225. doi: 10.1037/0096-3445.137.2.201

Giancola, P. R., and Mezzich, A. C. (2000). Neuropsychological deficits in female adolescents with a substance use disorder: better accounted for by conduct disorder? *J. Stud. Alcohol* 61, 809–817. doi: 10.15288/jsa.2000.61.809

Goschke, T. (2014). Dysfunctions of decision-making and cognitive control as transdiagnostic mechanisms of mental disorders: advances, gaps and needs in current research. *Int. J. Methods Psychiatr. Res.* 23, 41–57. doi: 10.1002/mpr.1410

Grace, J., and Malloy, P. F. (2001). *Frontal Systems Behavioral Scale (FrSBe): Professional Manual*. Lutz, FL: Psychological Assessment Resources.

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Res.* 18, 1279–1296. doi: 10.1016/0042-6989(78)90218-3

Handy, T. C. (2005). *Event-Related Potentials*. Cambridge, MA: The MIT Press.

Janssen, G. T. L. (2013). *Diagnostic Assessment of Psychiatric Patients: A Contextual Perspective on Executive Functioning*. Nijmegen: Donders Series.

Jockers-Scherübl, M. C., Wolf, T., Radzei, N., Schlattmann, P., Rentzsch, J., Gomez-Carrillo de Castro, A., et al. (2007). Cannabis induces different cognitive changes in schizophrenic patients and in healthy controls. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31, 1054–1063. doi: 10.1016/j.pnpbp.2007.03.006

Luijten, M., Machielsen, M. W. J., Veltman, D. J., Hester, R., de Haan, L., and Franken, I. H. A. (2013). Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *J. Psychiatry Neurosci.* 39, 149–169. doi: 10.1503/jpn.130052

Marshall, D. F., Walker, S. J., Ryan, K. A., Kamali, M., Saunders, E. F. H., Weldon, A. L., et al. (2012). Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder. *Psychiatry Res.* 200, 252–257. doi: 10.1016/j.psychres.2012.06.013

Mayr, U., and Kliegl, R. (2000). Task-set switching and long-term memory retrieval. *J. Exp. Psychol. Learn. Mem. Cogn.* 26, 1124–1140. doi: 10.1037//0278-7393.26.5.1124

Miyake, A., Emerson, M. J., Padilla, F., and Ahn, J. C. (2004). Inner speech as a retrieval aid for task goals: the effects of cue type and articulatory suppression in the random task cuing paradigm. *Acta Psychol.* 115, 123–142. doi: 10.1016/j.actpsy.2003.12.004

Miyake, A., and Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: four general conclusions. *Curr. Dir. Psychol. Sci.* 21, 8–14. doi: 10.1177/0963721411429458

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., and Howerter, A. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., and The Prisma Group (2009). Preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. *PLoS Med.* 6:e1000097. doi: 10.1371/journal.pmed1000097

Morris, N., and Jones, D. M. (1990). Memory updating in working memory: the role of the central executive. *Br. J. Psychol.* 81, 111–121. doi: 10.1111/j.2044-8295.1990.tb02349.x

Mueser, K. T., Drake, R. E., and Wallach, M. A. (1998). Dual diagnosis: a review of etiological theories. *Addict. Behav.* 23, 717–734. doi: 10.1016/S0306-4603(98)00073-2

Mueser, K. T., Noordsy, D. L., Drake, R. E., and Fox, L. (2011). *Geïntegreerde Behandeling Van Dubbele Diagnose. Een Richtlijn Voor Effectieve Behandeling*. Utrecht: de Tijdstroom.

Rabin, R. A., Zakzanis, K. K., and George, T. P. (2011). The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. *Schizophr. Res.* 128, 111–116. doi: 10.1016/j.schres.2011.02.017

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., et al. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area study. *JAMA* 264, 2511–2518. doi: 10.1001/jama.264.19.2511

Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Percept. Motor Skills* 8, 271–276. doi: 10.1080/13803395.2015.1052732

Rinck, M., Telli, S., Kampmann, I. L., Woud, M. L., Kerstholt, M., Velthuis te, S., et al. (2013). Training approach-avoidance of smiling faces affects emotional vulnerability in socially anxious individuals. *Front. Hum. Neurosci.* 7:481. doi: 10.3389/fnhum.2013.00481

Robbins, T. W., James, M., Owen, A. M., Sahakian, B. J., Mc Innes, L., and Rabbitt, P. (1994). Cambridge neuropsychological test automated battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia* 5, 266–281. doi: 10.1159/000106735

Roberts, R. J., Hager, L. D., and Heron, C. (1994). Prefrontal cognitive processes: working memory and inhibition in the antisaccade task. *Gen. J. Exp. Psychol.* 123, 374–393. doi: 10.1037/0096-3445.123.4.374

Rodriguez-Jimenez, R., Aragües, M., Jiminez-Arriero, M. A., Ponce, G., Martinez, I., Hoenicka, J., et al. (2008). Psychopathology and Wisconsin card sorting test performance in male schizophrenic patients: influence of Dual Diagnosis. *Psychopathology* 41, 58–64. doi: 10.1159/000110627

Rodriguez-Jiminez, R., Bagney, A., Martinez-Gras, I., Ponce, G., Sanchez-Morla, E. M., Aragües, M., et al. (2010). Executive function in schizophrenia: influence of substance use disorder history. *Schizophr. Res.* 118, 34–40. doi: 10.1016/j.schres.2009.09.0259

Rogers, R. D., and Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Gen. J. Exp. Psychol.* 124, 207–231. doi: 10.1037/0096-3445.124.2.207

Schnell, T., Koethe, D., Daumann, J., and Gouzoulis-Mayfrank, E. (2009). The role of cannabis in cognitive functioning of patients with schizophrenia. *Psychopharmacology* 205, 45–52. doi: 10.1007/s00213-009-1512-9

Sevy, S., Burdick, K. E., Visweswaraiah, H., Abdelmessih, S., Lukin, M., Yechiam, E., et al. (2007). Iowa gambling task in schizophrenia and co-occurring cannabis use disorders. *Schizophr. Res.* 92, 74–84. doi: 10.1016/j.schres.2007.01.005

Sharbanee, J. M., Hu, L., Stritzke, W. G., Wiers, R. W., Rinck, M., and MacLeod, C. (2014). The effect of approach/avoidance training on alcohol consumption is mediated by change in alcohol action tendency. *PLoS ONE* 9:e85855. doi: 10.1371/journal.pone.0085855

Smith, J. L., Mattick, R. P., Jamadar, S. D., and Iredale, J. M. (2014). Deficits in behavioural inhibition in substance abuse and addiction: a meta-analysis. *Drug Alcohol Depend.* 145, 1–33. doi: 10.1016/j.drugalcdep.2014.08.009

Snyder, H. R., Miyake, A., and Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gab between clinical and cognitive approaches. *Front. Psychol.* 6:328. doi: 10.3389/fpsyg.2015.00328

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi: 10.1037/0096-3445.121.1.15

Thoma, P., and Daum, I. (2013). Comorbid substance use disorder in schizophrenia: a selective overview of neurobiological and cognitive underpinnings. *Psychiatry Clin. Neurosci.* 67, 367–383. doi: 10.1111/pcn.12072

Van Gorp, W., Altshuler, L., Theberge, D. C., Wilkins, J., and Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence: a preliminary study. *Arch. Gen. Psychiatry* 55, 41–66. doi: 10.1001/archpsyc.55.1.41

Verdejo-Garcia, A., Bechara, A., Recknor, E. C., and Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. *J. Int. Neuropsychol. Soc.* 12, 405–415. doi: 10.1017/S1355617706060486

Verstraete, A. G. (2004). Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther. Drug Monit.* 26, 200–205. doi: 10.1097/00007691-200404000-00020

Walvoort, S., Wester, A. J., and Egger, J. I. M. (2013). Neuropsychologische diagnostiek en cognitieve functies bij alcoholabstinentie. *Tijdschr. Voor Psychiatr.* 55, 101–111.

Weeda, M. R., Peters, B. D., De Haan, L., and Linszen, D. H. (2006). Blijvende neuropsychologische stoornissen en structurele en functionele hersenafwijkingen na langdurig cannabisgebruik. *Tijdschr. Voor Psychiatr.* 48, 185–193.

Wiers, R. W., Cousijn, J., Mors-Schulte, M., den Uijl, T., Goudriaan, A., Schilt, T., et al. (2012). *State of the Art Neurocognitieve Effecten van Verslaving*. Den Haag: ZonMW.

Wiers, R. W., Rinck, M., Dictus, M., and van den Wildenberg, E. (2009). Relatively strong automatic appetitive action-tendencies in male carriers of the OPRM1G-allele. *Genes Brain Behav.* 8, 101–106. doi: 10.1111/j.1601-183X.2008.00454.x

Wiers, R. W., Rinck, M., Kordts, R., Houben, K., and Strack, F. (2010). Retraining automatic action-tendencies to approach alcohol in hazardous drinkers. *Addiction* 105, 279–287. doi: 10.1111/j.1360-0443.2009.02775.x

World Health Organisation [WHO] (2011). *Global Status Report on Alcohol and Health*. Geneva: WHO Press.

Yntema, D. B. (1963). Keeping track of several things at once. *Hum. Fact.* 5, 7–17. doi: 10.1177/001872086300500102

Ziedonis, D., and Brady, K. (2005). Dual diagnosis in primary care: detecting and treating both the addiction and mental illness. *Med. Clin. N. A.* 81, 1017–1036. doi: 10.1016/S0025-7125(05)705617

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REVIEW
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Disentangling Working Memory Functioning in Mood States of Bipolar Disorder: A Systematic Review

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Working memory (WM) deficits are often reported in patients with Bipolar Disorder (BD). However, it is not clear about the nature of these WM deficits (update or serial order processes) and their association with each BD states (euthymic, mania, and depressive). This review investigated the association between BD patient's states and the functioning of WM components. For this purpose, we carried out a systematic review fulfilling a search in the databases Medline, Scopus, SciELO, and Web of Science using specific terms in the abstracts of the articles that generated 212 outcomes in the restricted period from 2005 to 2016. Twenty-three papers were selected, completely read, and analyzed using PICOS strategy. The mood episodes predicted deficits in different components of WM in BD patients (the phonological loop or visuospatial sketchpad) and were associated with different WM processes (updating and serial recall). Lower cognitive scores persist even in remission of symptoms. This result suggests that WM deficit apparently is stage-independent in BD patients. Furthermore, findings suggest that the neutral point on Hedonic Detector component of WM could be maladjusted by BD.

Keywords: emotion, working memory, bipolar disorder, hedonic detector, mood states

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INTRODUCTION

Bipolar Disorder (BD) is a severe and chronic disorder characterized by emotional and humoral dysregulation that leads to increased frequency of cognitive dysfunction and interpersonal problems (Chang et al., 2012). BD type I is characterized by one mania episode or rapid (daily) cycling episodes of mania and depression, preceded or followed by hypomanic or major depressive episodes, presenting euphoria and exaggerated behaviors such as glibness, greatness, flight of ideas, leading to social problems. In type II, at least one hypomanic episode alternates with depression phases, occurring less externalizing problems compared to mania episodes regarding to mood switching, interpersonal, and occupational problems (American Psychiatric Association, 2013). It has estimated that BD rank is the 17th cause of years lived with disability in Europe, accounting for 1.6% of the total (World Health Organization, 2016). In the United States 2.6% of adults are affected by BD (National Institute of Mental Health, 2011) and in developing countries like Brazil ∼1% of the population are diagnosed with BD type I and II (Lima et al., 2005).

In addition to mood changes, patients with BD tend to show deficits in executive functions, verbal and visuospatial episodic memory, working memory (WM), verbal learning, information processing speed, sustained attention, and sensorimotor performance (Bora et al., 2009; Latalova et al., 2011; Lage et al., 2013; Loschiavo et al., 2013; Lee et al., 2014; Neves et al., 2014). Some studies have suggested more severe cognitive deficits in episodes of manic/mixed mood compared with depressive and euthymic episodes (Sweeney et al., 2000). Latalova et al. (2011) also observed that cognitive deficits tend to persist even in euthymic episodes, whereas, lower scores for verbal short-term memory and executive functions were found in both types of BD mood episodes, in tasks of WM, executive control, and verbal fluency. Some studies have shown that cognitive deficits observed in acute manic and depression episodes (Rubinsztein et al., 2000; Clark et al., 2001; Murphy, 2001), are also present in euthymic periods (van Gorp et al., 1998; Martinez-Aran et al., 2007; Wingo et al., 2009). Moreover, lower cognitive scores persist in visuospatial memory, verbal short and long-term memory, executive function, attention/processing speed, and WM, even after a long period of symptoms remission (van Gorp et al., 1998; Rubinsztein et al., 2000; Robinson et al., 2006; Martinez-Aran et al., 2007; Torres et al., 2007; McKenna et al., 2013; Ajilore et al., 2015). Besides that, first-episode BD is associated with widespread cognitive dysfunction (Lee et al., 2014), this result indicates cognitive deficits even in the earliest stages of disease and reinforces them as primary characters of BD. Symptoms of BD as anxiety and depression seem to reflect the malfunctioning of systems that provide a basis for action within a complex emotionally valenced world (Baddeley, 2013).

Among the cognitive deficits reported, WM seems to be relevant to understand the symptoms of BD. According to Miyake and Shah (1999) there are at least 10 diverse frameworks pointing different nature, structure, and functions of WM, which could diverge in terms of explanations of WM deficits. Then, it is important specifies some issues regarding this cognitive skill and its assessment that will be taken into account in the present paper. For instance, different tasks are considered measures of WM components: simple span tasks as measures of verbal and visuospatial storages, whereas, complex span tasks combine storage and attentional control (Baddeley, 1986). Currently, complex span tasks and n-back tasks are the most used WM measures (Miyake and Shah, 1999), since both require storing and maintain the information of a set of stimuli, and inhibiting interference of the signals recently presented (St Clair-Thompson and Gathercole, 2006). But there are dissimilarities, complex span tasks request keeping a serial order in mind at the same time of an ongoing cognitive task (Daneman and Merikle, 1996; Unsworth and Engle, 2007; Conway and Kovacs, 2013), while n-back tasks demand a constant updating of the relevant information (Kane et al., 2008; Wilhelm et al., 2013; Remoli and Santos, 2017). Apart from that, there are low correlations between n-back tasks and complex span tasks leading a conclusion that both evaluate different processes of WM (Kane et al., 2008; Redick and Lindsey, 2013), particularly concerning to the influence of emotional states (Ribeiro et al., submitted). A systematic review showed that different verbal WM capacities could be observed in studies that used mood induction before the completion of the task. While positive and negative stimuli seem to decrease the span task performance, no effects were found for n-back tasks (Ribeiro et al., submitted). In fact, negative mood induction can decrease WM performance during simple span and complex tasks (Spies et al., 1996; Santos et al., 2015; Soares, 2015).

In this review, WM is assumed to be a temporary information storage system that underpins the capacity for active thought by providing a cognitive workspace in which information may be temporarily maintained and manipulated (Baddeley, 2013). It is composed of multiple components, as the central executive, responsible for attentional control, and two subsidiary systems: the phonological loop and the visuospatial sketchpad, responsible for storing auditory-verbal and visual-spatial information, respectively (Baddeley et al., 2012). Subsequently, the episodic buffer was added to the initial WM model for integrating information from its multiple components with long-term memory (Baddeley, 2000). Previous studies indicated that when emotions and valenced thoughts are brought to WM they elicit somatic states (Bechara and Damasio, 2005), and the activation in brain emotional circuits, as conscious experience (LeDoux, 2000).

In fact, the connection of emotional states and working memory goes beyond the measurement instruments but in theoretical framework as well. For instance, the somatic marker hypothesis presented by Damasio et al. (1991) describes a mechanism for interaction between emotion and cognition in trial and decision-making processes (Bechara and Damasio, 2002, 2005; Bechara et al., 2005; Verdejo-García and Bechara, 2009). Damasio goes further by stating that the central executive component of working memory could be relevant in this process. As far as we know Baddeley's is the only model of WM explicitly addressing the capacity to temporary manipulate stored hedonic information. Baddeley proposed a new component, the Hedonic Detector which is understood as a neutral point that varies between positive and negative valences in response to environmental stimuli by establishing a mean value between stimulus and information retained in the WM to enable choices of future actions (Baddeley, 2007). It means that processing "hot" information (emotional content) disrupt the functioning of "cold" cognitive process, like core WM processes. Accounting this assumption, Baddeley et al. (2012) demonstrated that hedonic judgment of stimuli, such as words, pictures, and faces indeed could be influenced by the valence of an induced mood. Recently, different studies observed that mood induction procedures, e.g., listening valenced instrumental music while retrieving valenced autobiographical memories affect scores in WM tasks of health controls (e.g., Spachtholz et al., 2014; Allen et al., 2015). In this perspective, improper adjustment of the neutral point could be expressed by deficits to maintain, manipulate, and/or update information in WM. In the case of pathological affective episodes likewise in Bipolar Disorder (BD), the episodes itself could uncalibrated the hedonic detector.

Deficits in WM processing have been consistently reported in euthymic patients (MacQueen et al., 2005; Thompson et al., 2007; Daglas et al., 2015). Another study also observed that euthymic BD type I had worse performance on visuospatial

tasks compared to healthy subjects (Farahmand et al., 2015). Although, there is no consensus in the literature, these findings suggest that deficits in WM could result from the intensification of emotional valences. In other words, the presence of WM deficits, could be considered a primary trace of BD, beyond state variables (Gruber et al., 2009; Kurtz and Gerraty, 2009). However, this particular issue remains controversial due to the diversity of methodologies used across the studies. In addition to the prevalence of within-subjects design, some authors rarely made the connection between theoretical models and cognitive tasks, limiting the comprehension about WM and their particular components.

In line with this argument, a review by Baddeley (2013) showed that in depressive patients negative mood influences hedonic judgment, explaining the trend of the negative perception of the situations in this clinical population. However, there is no significant evidence in respect to the influence of positive mood in hedonic detection system. Hypothetically, assuming that the neutral point in BD patients corresponds to euthymic phase, the exacerbated positive and negative valences would account for euphoric or depressed mood, respectively (Baddeley, 2007, 2013). As emotion in BD is deregulated, the study of this disorder seems to be necessary to understand the influence of improper adjustment of the hedonic detector neutral point in WM.

There are many meta-analyses which state significant neuropsychological deficits in euthymic bipolar patients (Robinson et al., 2006; Torres et al., 2007; Bora et al., 2009; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011) and their relatives (Balanzá-Martínez et al., 2008; Arts et al., 2009; Bora et al., 2009). Most of these studies including working memory performance in bipolar patients Robinson et al. (2006), Torres et al. (2007), and Kurtz and Gerraty (2009) found that BD patients present deficits in measures of verbal working memory. In a recent review, Cullen et al. (2016) found similar results pointing that BD patients performed worse than controls in attention/working memory tasks. Bora et al. (2011) found evidences of verbal working memory deficits both in Type I and II bipolar patients. These deficits are found even in BD's relatives suggesting that these deficits are potential endophenotypes in Bipolar disorder; (Balanzá-Martínez et al., 2008; Arts et al., 2009) found evidences of worse performance in verbal working memory tasks in both BD's patients and relatives. Nonetheless these WM deficits are heterogeneous and seems to be affected by both demographic (e.g., educational level) and clinical aspects of the disorder (e.g., number of episodes) (Arts et al., 2009; Kurtz and Gerraty, 2009).

More recently, some studies using meta-analytical methodology addressed specific cognitive deficit in the bipolar patient as in theory of mind (Bora et al., 2016), social cognition (Samamé et al., 2015), and verbal fluency (Raucher-Chéné et al., 2017). Nonetheless, we did not found studies focusing in working memory deficits in bipolar disorder patients. Most of systematic review consider working memory in comparison to another cognitive functioning and some of than considered these deficits together with another executive functioning component (Robinson et al., 2006; Torres et al., 2007) and even attentional functioning (Cullen et al., 2016). Therefore, the purposes of this study are (i) to update the knowledge of working memory deficits including recent published data about working memory deficits in bipolar patients; (ii) analyze if BD patients show WM deficits, contrasting studies that used complex span tasks and n-back tasks; (iii) to investigate if different BD mood episodes predict different patterns of WM functioning, analyzing its components in each mood phase. The primary hypothesis of the present review is that working memory deficits are worsened during active phases of the disorder but remains in euthymic patients.

METHODS

This study is a descriptive and informative systematic review of the literature about the association between BD patient's states and the functioning of WM components. We used the instructions of Cochrane Foundation (Higgins and Green, 2011) to ensure the presentation of comprehensive and unbiased data. The following questions were asked to guide the review: Do patients diagnosed with BD have deficits in working memory? Are specific states of BD (mania, hypomania, depression, and euthymic) related to changes in working memory processes, such as updating and serial recall?

After the definition of the guiding questions, the following steps were taken: setting and collection of studies in databases; critical evaluation of studies, data selection and analysis, presentation, and interpretation of results (Bento, 2014).

All articles indexed in MEDLINE, Scopus, SciELO, and web of Science search databases that used, at least, one WM task in patients with BD, during a specified mood episode were included. Papers with available abstracts and written in Portuguese, English, or Spanish were considered.

Selected articles evaluated the WM in adult patients with BD, aged from 18 to 65 years old, and published until 15st July 2016. Literature reviews, case studies, and studies that referred to psychological or pharmacological interventions were excluded. Research and selection of manuscripts were done by the first author (CSF) and reviewed by the second author (FHS), with agreement between them.

For searches in databases, the terms "*transtorno bipolar*," "*memória operatória,*" and "*emoção*"; "*trastorno bipolar*," *"memoria operativa," and "emoción"*; and "bipolar disorder," "working memory," and "emotion" were used. We found 55 papers in MEDLINE, 63 in Scopus, 1 in Scielo, and 95 in Web of Science in the first search until 15th July 2016. No studies were found in Portuguese and only one study was written in Spanish.

Among the 214 papers identified, 34 were repeated, and 20 were found in more than two databases. Based on the abstract reading, from the 160 remaining studies 25 papers were selected and 135 were excluded, due to the presented criteria: (1) 16 did not use WM tasks; (2) 42 referred to literature reviews; (3) 27 had samples whose participants were under 18- or over 65-years old; (4) eight evaluated the effectiveness of psychological or pharmacological interventions; (5) three were animal sample studies; (6) 39 had undiagnosed BD participants.

Twenty-five articles were thoroughly analyzed, being excluded two studies for the following reasons: (1) the lack of contrast

between WM measures and non-social domains, which were used only as demographic control measures; (2) absence of description about the measures of WM and other cognitive domains in this session. As a result, 23 papers were discussed in this review (**Figure 1**).

Since most studies were methodologically unrelated to each other, carry out a meta-analysis in the present state of art would be premature, therefore we opted to systematically organize the selected articles hoping that this effort will provide new insights for researchers in order to advance in this field. Therefore, the current systematic review structured the analyses focused on the three main working memory processes (maintenance, manipulation, and updating), in respective modalities (verbal or non-verbal). The fundamental aspects of the papers were organized using the PICOS strategy, an acronym that represents the initials of the items: Population, Intervention (procedure), Comparison, Outcome, and Study Design (Bento, 2014). In this way, we used the following topics: population, type of intervention, methodological design, evaluated variables or expected results, and study design (**Table 1**). Based on these items

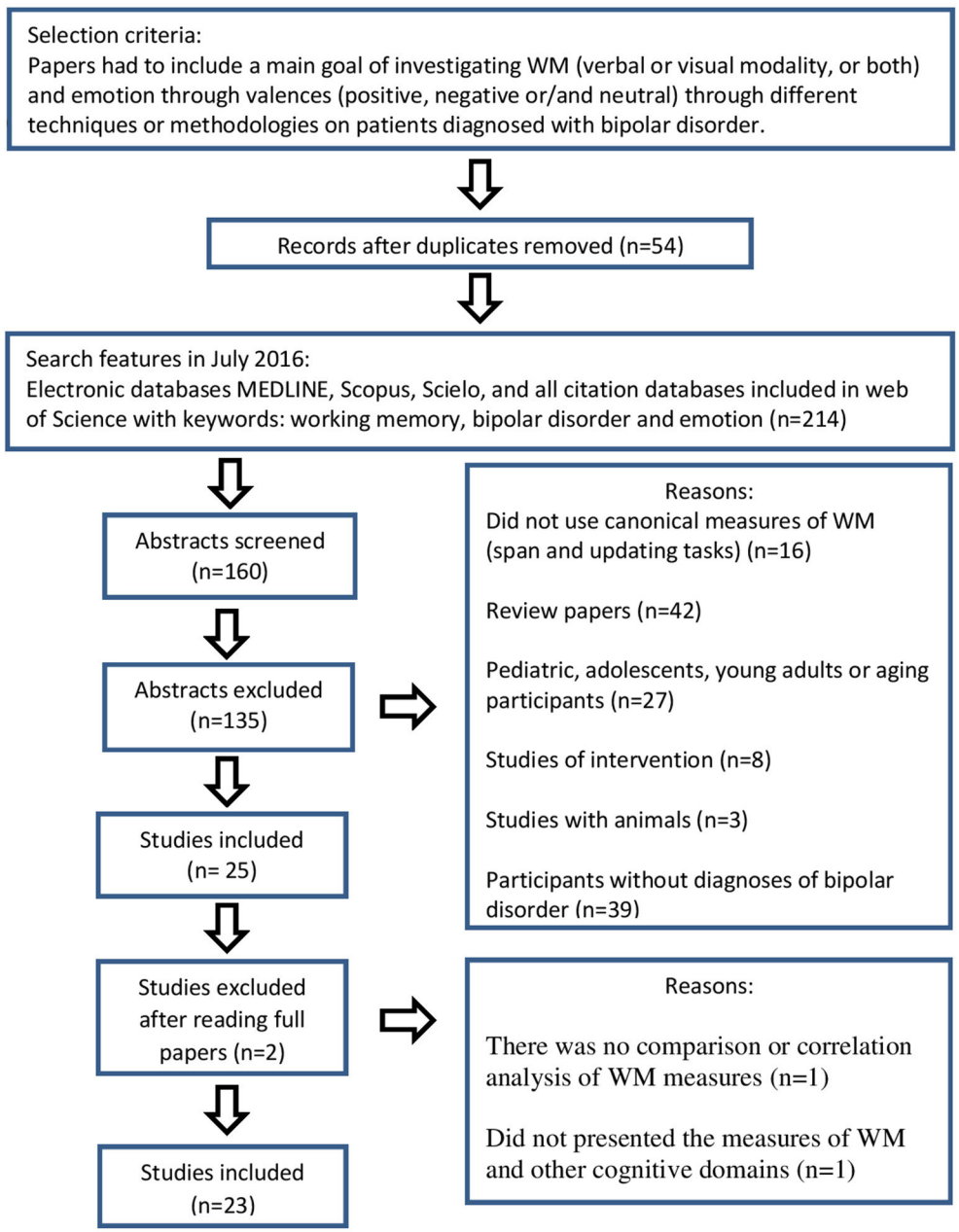

FIGURE 1 | Flowchart of search criteria and articles included in this review. WM, working memory.

TABLE 1 | Summary of selected articles with have investigated WM performance in BD subjects.

Article	Population	Intervention	Comparison	Outcome	Study design
Liu et al., 2010	*N* = 14 BD I, mean age 35.6 (10.9); *N* = 13 BD II, mean age 35.1 (9.8); *N* = 21 controls, mean age 38.3 (11.9)	Neuropsychological and behavioral assessment combined with physiological parameters	Cerebral white matter patterns and cognitive functioning correlation between groups	BD I: alterations in the right hemisphere. BD II: lower scores associated with cognitive and emotional processes. Brain alterations correlated with deficits of WM and executive function in both subtypes	Quantitative cross-sectional study
Bertocci et al., 2011	*N* = 23 unipolar depression (UD), mean age 29.74 (8.22); *N* = 18 BD I in depressive phase, mean age 31.94 (8.54); *N* = 16 controls, mean age 32.76 (6.50)	Neuropsychological and behavioral assessment combined with physiological parameters	Brain monitoring using fMRI during the tasks	Higher activity of dAMCC in UD, controls and BD I groups were found during 2-back neutral faces tasks	Quantitative cross-sectional study
Deckersbach et al., 2008	*N* = 9 BD I in moderated depressive phase, mean age 27.6 (2.8); *N* = 17 controls, mean age 25.6 (5.9)	Neuropsychological and behavioral assessment combined with physiological parameters	Sadness state induction using autobiographical memory and brain monitoring using fMRI during the tasks	BD I: greater activation in the left DLPFC and dACC in sadness condition	Prospective
Lee et al., 2013—1	*N* = 68 euthymic BD, mean age 43.9 (10.6); *N* = 38 schizophrenia in remission, mean age 44.7 (9.1); *N* = 36 controls, mean age 41.4 (9.9)	Neuropsychological and behavioral assessment	Social cognitive performance among clinical sample subgroups and controls	No significant difference in social cognitive performance between BD and control groups	Quantitative cross-sectional study
Lee et al., 2013—2	Same as Lee et al., 2013—1	Same as Lee et al., 2013—1	Social and nonsocial cognitive patterns among clinical groups	BD group had similar performance to controls in all areas. BD: more nonsocial than social deficit. Schizophrenia showed the opposite pattern	Same as Lee et al., 2013—1
Lee et al., 2013—3	*N* = 68 euthymic BD, mean age 43.9 (10.6); *N* = 38 schizophrenia in remission, mean age 44.7 (9.1)	Same as Lee et al., 2013—1	Comparison of social and nonsocial cognitive performance inter-clinical groups	Schizophrenia: more social cognitive deficits. BD: more nonsocial cognitive deficits	Idem
Levy et al., 2011	*N* = 82 euthymic BD I: 22 readmitted to the hospital, mean age 39.9 (12.7); 60 outpatient care, mean age 38.4 (11.6)	Neuropsychological and behavioral assessment	Mood state and cognitive performance before discharge and after 3 months inter-groups	Readmitted group: severe mood episodes and lower scores for executive function, attention and WM, visual and verbal episodic memory performance	Cohort prospective study
Miguélez-Pan et al., 2014	*N* = 31 euthymic BD, mean age 41.3 (11.1); *N* = 25 controls, mean age 40.40 (9.7)	Neuropsychological and behavioral assessment	Descriptive analysis of executive and functional profile and comparison of results inter-groups	BD: worse performance in flexibility, plan implementing, set-shifting and verbal fluency. No significant differences in WM	Descriptive cross-sectional study
Pomarol-Clotet et al., 2014	*N* = 38 BD I in mania state, mean age 39.74 (11.3); *N* = 38 BD in depression state - 32 BD I and 6 BD II - mean age 39.89 (10.39); 38 euthymic BD I, mean age 40 (8.7); *N* = 38 controls, mean age 39.68 (8.8)	Neuropsychological and behavioral assessment combined with physiological parameters	Brain monitoring using fMRI during cognitive the tasks in different mood phases	BD patients in depressive and manic phases showed worse performance in WM and lower activation in prefrontal dorsolateral and parietal cortex compared to controls; also in parietal cortex comparing to euthymic group. Mania group reported lower activation in left prefrontal dorsolateral cortex than euthymic group	Quantitative cross-sectional study
Roiser et al., 2009	*N* = 49 BD unmedicated in depression, majority BD II, mean age 33.6 (8.9); *N* = 55 controls, mean age 34.9 (8.1)	Neuropsychological and behavioral assessment combined with physiological parameters	Cognitive deficit inter-groups	BD: lower scores for short-term spatial memory, decision-making and insensitivity to negative feedback but not inattention, visual episodic memory and WM deficits	Quantitative cross-sectional study

(Continued)

TABLE 1 | Continued

Article	Population	Intervention	Comparison	Outcome	Study design
Thermenos et al., 2010	$N = 19$ euthymic BD, mean age 41.1 (3.1), $N = 18$ relatives without psychiatric diagnoses—RELs—mean age 36.6 (2.6); $N = 19$ controls, mean age 39.2 (2.7)	Neuropsychological and behavioral assessment combined with physiological parameters	Brain monitoring using fMRI during the tasks	BD and RELs: alterations in frontopolar cortex and insula during WM task. Correlations between brain activity, mood and WM	Quantitative cross-sectional study
Barrett et al., 2008	$N = 26$ euthymic. BD type I, mean age 52.50 (14.17); BD type II, mean age 41.43 (9.06); $N = 26$ controls, mean age 49.75 (13.11)	Neuropsychological and behavioral assessment	Cognitive deficit inter-groups and gender; cognitive performance intra-individual correlation	BD: greater visuospatial WM and verbal fluency low score. Deficits were more detectable in men compared to women, but both had similar number of errors	Quantitative cross-sectional study
Bauer et al., 2015	$N = 90$ euthymic BD, mean age 35.18 (1.3): 59 BD I, 28 BD II, 3 BD not specified; $N = 56$ controls, mean age 36.17 (1.9)	Neuropsychological and behavioral assessment	Cognitive deficit inter-groups and intra-individual correlation	BD: no affective short-term memory and verbal fluency deficit. No significant difference in WM	Quantitative cross-sectional study
Dittman et al., 2008	$N = 74$ euthymic BD—52 BD I and 23 BD II—mean age 42.52 (12.23); $N = 42$ controls, mean age 43.02 (12.75)	Neuropsychological and behavioral assessment combined with physiological parameters	Level of homocystein inter-groups and cognitive performance and level of homocystein intra-individual correlation	BD: deficit in all cognitive tasks, including WM deficits	Quantitative cross-sectional study
Drapier et al., 2008	$N = 20$ BD I, mean age 42.7 (10.4); $N = 20$ relatives without substitute TAB for BD, mean age 43 (13.8); $N = 20$ controls, mean age 41.9 (11.6)	Neuropsychological and behavioral assessment combined with physiological parameters	Brain monitoring using fMRI during the tasks	BD: lower WM scores compared to control and relative groups. BD and relative groups: more prefrontal cortex activity	Quantitative cross-sectional study
Fleck et al., 2005	$N = 26$ BD I hospitalized in mania/ mixed + psychotic symptoms, mean age 28 (7); $N = 23$ euthymic BD outpatient care, mean age 28 (7); $N = 28$ controls, mean age 28 (9)	Neuropsychological and behavioral assessment	Cognitive performance, reaction time and sensitivity perceptual correlation inter-groups	Manic BD group showed recognition effectiveness and directed-forgetting effectiveness deficit. The BD group needed more effort to encode information	Quantitative cross-sectional study
Gruber et al., 2013	$N = 29$ euthymic BD I, mean age 30.28 (8.7); $N = 29$ major depression in remission, mean age 31.32 (11.32); $N = 30$ controls, mean age 31.45 (9.3).	Neuropsychological and behavioral assessment.	Negative and positive mood maintainability capacity; and WM correlation inter-groups	BD I: affective WM deficit compared to other groups. No difference between euthymic and control groups	Quantitative cross-sectional study
Malhi et al., 2007	$N = 10$ euthymic BD I, mean age 32.4 (10.8); $N = 10$ controls, mean age 31.7 (11.9)	Neuropsychological and behavioral assessment combined with physiological parameters	Brain monitoring using fMRI during the tasks on different mood valences	Control group: increased activation in medial prefrontal cortex, medial frontal cortex and right parahippocampal gyrus during positive and negative valences induction. No difference in reaction time and accuracy	Quantitative cross-sectional study
Mullin et al., 2012	$N = 22$ euthymic BD I, mean age 31.68 (8.9); $N = 19$ controls, mean age 32.54 (6.5)	Neuropsychological and behavioral assessment combined with physiological parameters	Brain monitoring using fMRI during the tasks	BD: (i) less activation in dorsolateral prefrontal cortex, dACC, and parietal cortex without emotional distractors; (ii) increased amygdala and striatum activity before negative stimuli; and (iii) greater connection activity in dACC and amygdala after positive stimuli	Quantitative cross-sectional study
Russo et al., 2014	$N = 64$ euthymic BD—77% BD I, 14% BD II and 9.4% not specified—mean age 41.2 (10.5); $N = 109$ controls, mean age 37.9 (11.6)	Neuropsychological and behavioral assessment	Mood state, temperament and cognition inter-groups and intra-individual correlation	BD: positive correlation in level of cyclotimia and irritability with information processing, WM, reasoning and problem solving	Quantitative cross-sectional study

(Continued)

TABLE 1 | Continued

Article	Population	Intervention	Comparison	Outcome	Study design
Thompson et al., 2007	*N* = 50 euthymic BD—44 BD I and 6 BD II—mean age 44.42 (8.6); *N* = 57 controls, mean age 44.86 (9.2).	Neuropsychological and behavioral assessment	Cognitive deficit inter-groups	BD: lower scores in Backward Digit Span. No difference in recognition task, visuospatial WM, Forward Digit Span and executive processes (verbal fluency; visual attention) between groups	Quantitative cross-sectional study
Muhtadie and Johnson, 2015	*N* = 27 euthymic BD I, mean age 35.63 (12.5); *N* = 24 controls, mean age 30.42 (11)	Neuropsychological and behavioral assessment combined with physiological parameters	Autonomic physiology and emotional reactions monitoring during the task	BD: high levels of emotional (anxiety) and autonomic (cardiovascular) reactivity, which were positively correlated	Quantitative cross-sectional study
Gvirts et al., 2015	*N* = 30 BD mildly affective symptoms, 26 BD I, 4 BD II, mean age 41.93 (12.94); *N* = 32 Borderline Personality Disorder (BPD), mean age 29.01 (9.28); matching a healthy control group	Neuropsychological and behavioral assessment	Cognitive performance inter-groups and correlation between sustained attention and cognitive measures	BD: deficits in strategy formation and planning execution time comparing to other groups; poorer utilization of strategy in the SWM task comparing to BPD. BPD: deficit in planning in comparison to all groups; in problem-solving comparing to controls. BD and BPD: deficits in sustained attention	Quantitative cross-sectional study
Sabater et al., 2016	*N* = 73 euthymic BD: 29 in lithium monotherapy (L), mean age 24.3 (9.3); 28 lithium + anticonvulsants (LA), mean age 26.8 (10.8); 16 in anticonvulsant therapy (A), mean age 28.6 (12.1); *N* = 25 controls	Neuropsychological and behavioral assessment	Comparison of cognitive performance between groups	BD-L: preserved short-term auditory memory, long-term memory, and attention. BD-A: worse performance in short-term visual memory, WM, and several executive functions. All BD patients: poorly in processing speed, resistance to interference, and emotion recognition	Quantitative cross-sectional study
McCormack et al., 2015	*N* = 99 high genetic risk (AR relatives), mean age 22.0 (4.5); *N* = 52 BD higher mood severity symptoms, 27 BD I, 25 BD II, mean age 24.6 (3.8); *N* = 78 controls, mean age 22.4 (3.9)	Neuropsychological and behavioral assessment	Comparison of cognitive performance between groups	AR: verbal reasoning and affective response inhibition deficits. BD: deficits in attention. Neither AR nor BD patients showed lower scores for general intellectual ability, WM, visuospatial or language ability. Only the BD participants showed impaired emotion recognition	Quantitative cross-sectional study

BD, Bipolar disorder; WM, working memory; REL, relatives; dAMCC, dorsal anterior midcingulate cortex; DLPFC, left dorsolateral prefrontal cortex; dACC, dorsal anterior cingulate cortex; fMRI, functional magnetic resonance imaging.

we could discuss them into three sessions: "Cognitive deficits and neurobiological correlates in BD patients," "Different patterns of cognitive processes in each mood phase," and "Relationship among WM and other clinical features." The first two items addressed clearly the objectives that motivated the present study and the final session account for other findings observed in the selected articles.

RESULTS

The *SCImago Journal & Country Rank* was used as an indicator of visibility in scientific domains by ranking the journals in which papers were published. The ranking for psychology, neuroscience, and medicine areas in the last 7 years were considered. Twenty-one studies were published in Q1 journals (Fleck et al., 2005; Malhi et al., 2007; Thompson et al., 2007; Barrett et al., 2008; Deckersbach et al., 2008; Drapier et al., 2008; Roiser et al., 2009; Liu et al., 2010; Thermenos et al., 2010; Bertocci et al., 2011; Levy et al., 2011; Mullin et al., 2012; Gruber et al., 2013; Lee et al., 2013; Pomarol-Clotet et al., 2014; Russo et al., 2014; Bauer et al., 2015; Gvirts et al., 2015; McCormack et al., 2015; Muhtadie and Johnson, 2015; Sabater et al., 2016), one in Q2 journal (Miguélez-Pan et al., 2014), and one in Q3 journal (Dittman et al., 2008). These quartiles also indicated that the majority of selected studies were published in higher impact factor journals.

According to the publication period of the selected articles, the first research of a direct association between emotions and WM in BD patients was performed by Fleck et al. (2005). The other studies were published in the following periods. The research studies have been mostly carried out in America, with eleven studies in the United States, eight in Europe, four of them in Asia.

Considering the first topic of analysis, most studies participants were subjects of both gender, except articles by Bertocci et al. (2011), Deckersbach et al. (2008), Malhi et al. (2007), and Thermenos et al. (2010) that only studied women. There were higher prevalence of studies with euthymic phase of BD samples, but three studies considered only depressive episodes in BD subjects (Deckersbach et al., 2008; Roiser et al., 2009; Bertocci et al., 2011). Furthermore, one paper compared a manic/psychotic symptoms group with a euthymic population (Fleck et al., 2005) and another one assessed three groups: mania, depression, and euthymic (Pomarol-Clotet et al., 2014). Articles by Liu et al. (2010) and McCormack et al. (2015) did not characterize explicitly the sample mood despite presented scores of symptoms scales and the study by Gvirts et al. (2015) comprised two subgroups with regard to affective symptoms: asymptomatic and mildly symptomatic patients. Regarding the subtypes of BD, 13 studies used BD I and II mixed groups, nine studies analyzed only BD type I subjects, and one paper compared BD type I, type II, and control groups (Liu et al., 2010).

Most studies evaluated the sample in just one mood episode in BD. Euthymic patients were predominant in the samples (Malhi et al., 2007; Barrett et al., 2008; Dittman et al., 2008; Drapier et al., 2008; Thermenos et al., 2010; Levy et al., 2011; Mullin et al., 2012; Gruber et al., 2013; Lee et al., 2013; Miguélez-Pan et al., 2014; Russo et al., 2014; Bauer et al., 2015; Muhtadie and Johnson, 2015; Sabater et al., 2016), few studies evaluated depressions phases of BD (Deckersbach et al., 2008; Roiser et al., 2009; Bertocci et al., 2011) and only one compared the performance in manic and euthymic episodes in relation to health controls (Fleck et al., 2005). All studies have used between-groups comparison, and only article by Pomarol-Clotet et al. (2014) also had a within-participants design and evaluated the same patients in three characteristics mood phases of BD.

Regarding the intervention, all studies used cognitive tests and self-reported mood scales. Seven studies (Malhi et al., 2007; Deckersbach et al., 2008; Drapier et al., 2008; Thermenos et al., 2010; Bertocci et al., 2011; Mullin et al., 2012; Pomarol-Clotet et al., 2014) also applied functional magnetic resonance imaging (fMRI) to measure brain activity. In relation to the cognitive instruments, 16 studies used span tasks (Malhi et al., 2007; Thompson et al., 2007; Barrett et al., 2008; Dittman et al., 2008; Roiser et al., 2009; Liu et al., 2010; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013; Miguélez-Pan et al., 2014; Russo et al., 2014; Bauer et al., 2015; Gvirts et al., 2015; McCormack et al., 2015; Muhtadie and Johnson, 2015; Sabater et al., 2016), and six studies chose n-back tasks (Deckersbach et al., 2008; Drapier et al., 2008; Thermenos et al., 2010; Bertocci et al., 2011; Mullin et al., 2012; Pomarol-Clotet et al., 2014), with two of them using the modified EFNBACK instrument. Only one article used a supra span task, the yes/no recognition memory test, based in verbal directed-forgetting paradigm. For the evaluation of mood symptoms, the most used instruments were: Young Mania Rating Scale (YMRS) for mania symptoms (Fleck et al., 2005; Malhi et al., 2007; Thompson et al., 2007; Barrett et al., 2008; Deckersbach et al., 2008; Dittman et al., 2008; Liu et al., 2010; Bertocci et al., 2011; Levy et al., 2011; Mullin et al., 2012; Gruber et al., 2013; Lee et al., 2013; Miguélez-Pan et al., 2014; Pomarol-Clotet et al., 2014; Bauer et al., 2015; Gvirts et al., 2015; McCormack et al., 2015; Sabater et al., 2016); Hamilton Depression Rating Scales (Fleck et al., 2005; Malhi et al., 2007; Thompson et al., 2007; Barrett et al., 2008; Deckersbach et al., 2008; Dittman et al., 2008; Liu et al., 2010; Bertocci et al., 2011; Mullin et al., 2012; Lee et al., 2013; Miguélez-Pan et al., 2014; Pomarol-Clotet et al., 2014; Russo et al., 2014; Gvirts et al., 2015; Sabater et al., 2016), Montgomery Åsberg Depression Rating Scale (Malhi et al., 2007; Roiser et al., 2009; Liu et al., 2010; Bauer et al., 2015; McCormack et al., 2015), and Beck Depression Inventory (Malhi et al., 2007; Thompson et al., 2007; Drapier et al., 2008; Muhtadie and Johnson, 2015) for depressive symptoms (**Table 2**).

Methodologies of selected studies were characterized by the comparison of cognitive variables and mood episodes between clinical and control groups. Seven articles carried just a comparison of cognitive profile between groups (Fleck et al., 2005; Thermenos et al., 2010; Levy et al., 2011; Miguélez-Pan et al., 2014; Pomarol-Clotet et al., 2014; McCormack et al., 2015; Sabater et al., 2016). In addition, eight studies evaluated correlation between variables, such as cognitive pattern and brain activation pattern (Liu et al., 2010), gender and cognitive pattern (Barrett et al., 2008), functionality, and cognition (Bauer et al., 2015), homocysteine levels and cognitive performance (Dittman

TABLE 2 | Summary of WM tasks, cognitive tests, behavioral, and physiological measures used in the selected articles.

Article	Working memory tasks	Cognitive tests	Behavioral measures	Physiological measures
Liu et al., 2010	Word retrieval test from Wechsler Memory Scale-III	Wisconsin Card Sorting Test (WCST); Test for Attention Performance (version 1.02)	Young Mania Rating Scale (YMRS), 17-item Hamilton Rating Scale for Depression (HAM-D-17), Montgomery Åsberg Depression Rating Scale (MADRS)	Fractional anisotropy (FA)
Bertocci et al., 2011	N-back (EFNBACK) task	–	HAM-D-25; YMRS	Functional magnetic resonance imaging (fMRI)
Deckersbach et al., 2008	N-back task	–	HAM-D; YMRS	fMRI
Lee et al., 2013	MATRICS Consensus Cognitive Battery (MCCB)	Facial affect recognition task; Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT); Empathic accuracy task; The Awareness of Social Inference Test, Part III (TASIT); Self-referential memory task	HAM-D; YMRS	–
Levy et al., 2011	Digit Span subtest from the Wechsler Adult Intelligence Scale—Third Edition	Trail Making Test (TMT); Controlled Oral Word Association Test (COWAT); Stroop Color-Word Interference Test; WCST; Wechsler Abbreviated Scale of Intelligence (WASI); Letter and Symbol Cancellation Task; California Verbal Learning Test II—Short Form; Logical Memory from Wechsler Memory Scale-R; Rey Complex Figure test (RCFT)	Beck Depression Inventory (BDI-II); YMRS.	–
Miguélez-Pan et al., 2014	WAIS-III Digits Forward; WAIS-III Digits Backward subtest	Token Test (TT); WAIS-III Vocabulary subtest; WCST-64; WAIS-III Similarities subtest; TMT; Tower of London-Drexel University; FAS; Five Point Test (5PT); Stroop Color and Word Test; Frontal Assessment Battery (FAB)	Global Assessment of Functioning (GAF); HAM-D; YMRS	–
Pomarol-Clotet et al., 2014	N-back task	–	YMRS; HAM-D	fMRI
Roiser et al., 2009	Cambridge Neuropsychological Test Automated Battery (CANTAB): Spatial Span, Spatial Working Memory test (SWM)	CANTAB: Intra-dimensional/Extra-dimensional Set-Shifting (ID/ED), Spatial Recognition Memory, Pattern Recognition Memory; Delayed Match to Sample, Rapid Visual Information Processing (RVIP), Cambridge Gamble task, Affective Go/No-go test (AGN), Probabilistic Reversal Learning	MADRS; Inventory of Depressive Symptomatology	–
Thermenos et al., 2010	Two-Back Working Memory Task	Control CPT-X Task; Vocabulary and Block Design subtests of the WAIS-R; reading subtest of the WRAT-R	Profile of Mood States (POMS)	fMRI
Barrett et al., 2008	CANTAB: SWM	CANTAB: Stocking of Cambridge test (SoC); (ID/ED); Set–Shifting task	HAM-D; YMRS	–
Bauer et al., 2015	Cognition in Affective Disorders (BAC-A): Digit Sequencing Task	BAC-A: Token Motor Task, Symbol Coding, List Learning, Category In-stances, Controlled Oral Word Association Test (F and S-words), Tower of London, Emotion Inhibition Test, affective auditory verbal learning test	GAF; MADRS; YMRS	–
Dittman et al., 2008	Wechsler Adult Intelligence Scale III (WAIS-III): Letter-Number Sequencing Subtest (LNST)	TMT; Repeatable Battery for the Assessment of Neuropsychological Status Form A (RBANS)	HAM-D; YMRS	–

(Continued)

TABLE 2 | Continued

Article	Working memory tasks	Cognitive tests	Behavioral measures	Physiological measures
Drapier et al., 2008	N-back working memory task	Baseline attention task	BDI; Altman Self-Rated Mania Scale (ASRM)	fMRI
Fleck et al., 2005	Yes/no recognition memory tests	CPT	YMRS; HAM-D; Scale for the Assessment of Positive Symptoms (SAPS)	–
Gruber et al., 2013	Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV): LNST; Affective Working Memory Task	Shipley Institute of Living Scale (SILS)	YMRS; Inventory of Depressive Symptomatology-Clinician Rating (IDS-C)	–
Malhi et al., 2007	Delayed-response working memory paradigm based on the Sternberg memory task	Extracted visual stimuli of Lang Affective Norms for English Words (ANEW) database	HAM-D-17; YMRS; MADRS; GAF; BDI	fMRI task with implicit affective content
Mullin et al., 2012	EFNBACK	–	HAM-D-25; YMRS	fMRI
Russo et al., 2014	MCCB	–	TEMPS-A; HAM-D; Clinician Administered Rating Scale for Mania (CARS-M)	–
Thompson et al., 2007	Digits Forwards; Backwards Digit Span	Self-Ordered Pointing Task –modified version (SOPT); CANTAB; Executive functions and WM tasks: Stroop, initial letter; FAS, TMT	HAM-D; YMRS; BDI ASRM	–
Muhtadie and Johnson, 2015	Automated Symmetry Span Task	–	Self-Reported Emotions; BDI–SF; ARSM	Cardiovascular Physiology
Gvirts et al., 2015	CANTAB: SWM	CANTAB: RVIP, CANTAB's version of the Tower of London task (ToL), ID/ED	HAM-D-17, YMRS, GAF; clinical global impression (CGI)	–
Sabater et al., 2016	Wechsler Memory Scale-Revised (WMSR)	WAIS-III, digit span; TMT-A and B; RCFT; WCST; Tower of Hanoi (TOH-4); Stroop color word test; FAB; Copy RCFT; Eye Test	Visual Analog Scale and the Spanish Version of the Chinese Polarity Inventory; HAM-D; YMRS; CGI-BP	–
McCormack et al., 2015	RBANS; WAIS-III: digit span task and letter–number sequencing tasks	Wechsler Abbreviated Scale of Intelligence; RBANS subscales; CANTAB: ID/ED, SoC, AGN; Ekman 60-Faces emotion recognition test; Awareness of Social Inference Test -A	Family Interview for Genetic Studies (FIGS); Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Bipolar Disorder version (K-SADS-BP); K-SADS (WASH-U-KSADS); Diagnostic Interview for Genetic Studies (DIGS); MADRS; Bipolar Depression Rating Scale (BDRS); YMRS; Children's Depression Inventory (CDI)	–

References of the instruments cited in the Table are available on the original articles.

et al., 2008), reaction time and perceptual sensitivity (Fleck et al., 2005), humor and WM (Gruber et al., 2013; Russo et al., 2014), and cognitive pattern (Gvirts et al., 2015). Two of the seven fMRI studies stand out, one described brain activation in different mood phases of BD (Pomarol-Clotet et al., 2014) and the other assessed brain effect of mood induction (Malhi et al., 2007). The article by Muhtadie and Johnson (2015) differ from others because combined evaluation of autonomic variables during WM performance (**Table 1**).

The results showed different brain patterns activity during the performance of WM tests. Most of the neuroimaging studies used n-back tasks to evaluate WM processing. Studies that chose the n-back paradigm found low left dorsal anterior midcingulate cortex (dAMCC) activation in depressive phase of BD type I group (Bertocci et al., 2011), low dorsolateral prefrontal and parietal cortex activation in depression and manic phases (Pomarol-Clotet et al., 2014), and low activity of dorsolateral prefrontal cortex, dorsal anterior cingulate cortex (dACC) and parietal cortex in euthymic group (Mullin et al., 2012). However, some studies have shown conflicting results, as greater prefrontal cortex activation in BD patients and their relatives (Drapier et al., 2008) as well as increased dorsolateral prefrontal cortex and dAMCC activity in episodes of depressed mood (Deckersbach et al., 2008). Low activations in prefrontal cortex in span tasks studies were also confirmed (Malhi et al., 2007; Liu et al., 2010; Thermenos et al., 2010). Article by Liu et al. (2010) indicated that BD type I subjects tend to show lateralized alterations in the right brain hemisphere, while BD type II presented more distributed deficits. In addition, BD patients and their relatives showed frontopolar cortex and insula brain alterations (Thermenos et al., 2010) and euthymic BD subjects exposed to positive and negative valences reported less activation in medial prefrontal cortex, medial frontal cortex, and right parahippocampal gyros (Malhi et al., 2007).

Regarding the cognitive performance of participants in WM tasks, 11 studies demonstrated lower performance in BD patients compared to control groups. Three studies involving processing of visuospatial information (Fleck et al., 2005; Barrett et al., 2008; Gvirts et al., 2015); six papers concerning auditory verbal processing (Dittman et al., 2008; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013; Pomarol-Clotet et al., 2014; Sabater et al., 2016); and one article studying updating of visuospatial information (Drapier et al., 2008). Concerning effect sizes reported on such articles we decided to analyze mean effect size on studies that produced lower scores for working memory performance. This descriptive analysis showed an average effect size of 0.39 to studies that involved processing of visuospatial information; and 0.41 to the papers concerning auditory verbal processing. The only paper that used measures of updating visuospatial information presented a effect size of 0.33. We can conclude that all the average effect sizes are low (Cohen, 1988). There are also nine papers (Malhi et al., 2007; Deckersbach et al., 2008; Drapier et al., 2008; Liu et al., 2010; Thermenos et al., 2010; Bertocci et al., 2011; Mullin et al., 2012; Pomarol-Clotet et al., 2014; Muhtadie and Johnson, 2015) that reported a variety of neurobiological changes in BD patients (e.g., prefrontal cortex activation or dorsal anterior cingulate cortex; see **Table 3**).

However, four studies found no difference between groups (Roiser et al., 2009; Miguélez-Pan et al., 2014; Bauer et al., 2015; McCormack et al., 2015). Article by Pomarol-Clotet et al. (2014) distinguished cognitive profiles according to the mood phases of patients, showing that manic or depressive episodes in BD reported worse performance in WM tasks compared with euthymic and controls groups. However, WM deficits (Thompson et al., 2007; Drapier et al., 2008) and other cognitive low scores can also be observed in euthymic phase, for example, visuospatial WM (Barrett et al., 2008), short-term non-affective memory (Bauer et al., 2015), unsocial cognition (Lee et al., 2013), flexibility, plan implementing, set-shifting (Miguélez-Pan et al., 2014), processing speed, resistance to interference and emotion recognition (Sabater et al., 2016), and verbal fluency (Barrett et al., 2008; Miguélez-Pan et al., 2014; Bauer et al., 2015). In addition, WM performance was associated with cyclothymic levels and irritability in euthymic episodes (Russo et al., 2014; **Table 3**).

Euthymic patients during conducted span tasks showed deficits in several WM components, such as auditory information updating (Thompson et al., 2007), simultaneous processing of visuospatial information (Barrett et al., 2008), and processing of auditory-verbal information (Thompson et al., 2007; Dittman et al., 2008; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013). BD type I patients also reported lower scores for updating visuospatial information during the n-back task (Drapier et al., 2008).

Some researches of euthymic samples used auditory-verbal complex span tasks (Miguélez-Pan et al., 2014; Bauer et al., 2015; Sabater et al., 2016). Nevertheless, clinical groups performed similarly to controls in processing auditory information (Miguélez-Pan et al., 2014; Bauer et al., 2015). Article by Roiser et al. (2009) also did not found deficits to perform a visuospatial span task in depressive episodes in BD patients during washout of psychotropic medications.

A prevalence of quantitative cross-sectional methodology experiment designs were characterized in selected articles (Fleck et al., 2005; Malhi et al., 2007; Thompson et al., 2007; Barrett et al., 2008; Dittman et al., 2008; Drapier et al., 2008; Roiser et al., 2009; Liu et al., 2010; Thermenos et al., 2010; Bertocci et al., 2011; Mullin et al., 2012; Gruber et al., 2013; Lee et al., 2013; Pomarol-Clotet et al., 2014; Russo et al., 2014; Bauer et al., 2015; Gvirts et al., 2015; McCormack et al., 2015; Muhtadie and Johnson, 2015; Sabater et al., 2016). Only three studies used other experimental designs, such as cohort study (Levy et al., 2011), descriptive study (Miguélez-Pan et al., 2014), and prospective study (Deckersbach et al., 2008) (**Table 1**).

DISCUSSION

The aims of the present systematic review were (i) update the knowledge about working memory deficits in BD; (ii) to analyze if BD patients show WM low scores, contrasting studies that used complex span tasks and n-back tasks, and (iii) to investigate if different BD mood episodes could predict different patterns of cognitive processes based on the WM components of the

TABLE 3 | Summary of WM performance and neurobiological changes in BD subjects in selected articles categorized according WM processes and modalities.

Article	Performance in WM tasks	WM processes and modalities	Effect size	Neurobiological alterations
Barrett et al., 2008	↓	Processing of visuospatial information	0.58 (r)	–
Fleck et al., 2005	↓	Processing of visuospatial information	0.23 (η)	–
Gvirts et al., 2015	↓	Processing of visuospatial information	0.21 (d)	–
Muhtadie and Johnson, 2015	–	Processing of visuospatial information	0.76 (d)	Autonomic changes associated with emotional reactivity during cognitive tasks
Roiser et al., 2009	=	Processing of visuospatial information	−0.16 (d)	–
Russo et al., 2014	WM performance was associated with cyclothymic levels and irritability in euthymic episodes	Processing of visuospatial and auditory-verbal information	0.54 (r)	–
Bauer et al., 2015	=	Processing of auditory-verbal information	–	–
Dittman et al., 2008	↓	Processing of auditory-verbal information	0.41 (d)	–
Gruber et al., 2013	↓	Processing of auditory-verbal information	0.26 (η)	–
Lee et al., 2013	↓	Processing of auditory-verbal information	0.61 (η)	–
Lee et al., 2013	↓	Processing of auditory-verbal information	0.61 (η)	–
Levy et al., 2011	↓	Processing of auditory-verbal information	0.56 (d)	–
Liu et al., 2010	–	Processing of auditory-verbal information	–	BD I: lateralized changes in the right hemisphere and more cognitivedeficits. BD II: more distributed deficits associated with cognitive and emotional processes
McCormack et al., 2015	=	Processing of auditory-verbal information	–	–
Miguélez-Pan et al., 2014	=	Processing of auditory-verbal information	−0.29 (d)	–
Sabater et al., 2016	↓ BD patients in anticonvulsant therapy	Processing of auditory-verbal information	0.16 (η)	–
Thompson et al., 2007	↓	↓ auditory information updating/ ↓ processing of auditory-verbal information	0.39 (d)	–
Bertocci et al., 2011	–	Updating visuospatial information	0.75 (d)	↓ dAMCC activation with neutral stimuli in depressive episodes
Deckersbach et al., 2008	–	Updating visuospatial information	0.07 (d)	↑ DLPFC and dACC activation when negative valence stimuli were presented
			0.03 (r)	
Drapier et al., 2008	↓	Updating visuospatial information	0.33 (η)	↓ prefrontal cortex activation
Malhi et al., 2007	–	Updating visuospatial information	–	↓ prefrontal cortex activation
Mullin et al., 2012	–	Updating visuospatial information	–	↓ prefrontal cortex activation
Pomarol-Clotet et al., 2014	↓ manic and depressive episodes	Updating visuospatial information	–	Parietal alterations in manic and depressive episodes
Thermenos et al., 2010	–	Updating visuospatial information	1.05 and 1.33 (d)	Frontopolar cortex and insula alterations brain

WM, working memory; dACC, dorsal anterior cingulate cortex; dAMCC, left dorsal anterior midcingulate cortex; DLPFC, left dorsolateral prefrontal cortex; BD, bipolar disorder; d, Cohen's d; n, Eta-squared; r, Pearson's correlation; =, no significant differences.

tasks in each mood phase. Considering the first objective our study found similar results to previous systematic review and meta-analyses pointing to working memory deficits in Bipolar patients (Robinson et al., 2006; Torres et al., 2007; Kurtz and Gerraty, 2009; Bora et al., 2011; Mann-Wrobel et al., 2011). Most of these reviews pointed to verbal working memory deficits in BD (Robinson et al., 2006; Torres et al., 2007; Kurtz and Gerraty, 2009). These findings could be explained by the fact that those reviews considered only digit span measures. In our review, we included both verbal and visuospatial working memory measures. In agreement with previous reviews, we found that both verbal and visuospatial working memory are impaired in BD (Bora et al., 2011; Mann-Wrobel et al., 2011).

Considering objective (ii) and (iii) they were respectively presented in Sections Introduction and Methods. This review seems to be necessary because individual results of studies are confusing, due to the fact that there are three emotional phases in BD (euthymic, euphoric, and depressed) and different WM mental operations (serial recall and update), which are expressed in at least two different modalities (phonological and visuospatial) (**Table 4**). For this purpose, after the selection of the articles according to the inclusion and exclusion criteria, a systematic review was carried out. Twenty-three studies in the restricted period 2005–2016 were found using different approaches as cognitive, behavioral, neuroimaging, and measures of autonomic responses. The study also convey the possibility of

TABLE 4 | Summary of mental WM operations and phonological and visuospatial modalities in three emotional phases in BD presented in the selected articles.

Modality/ task	Euthymic	Depressive	Manic
Verbal n-back	–	–	–
Visuospatial n-back	Malhi et al., 2007; Drapier et al., 2008; Mullin et al., 2012	Deckersbach et al., 2008; Pomarol-Clotet et al., 2014	Pomarol-Clotet et al., 2014
Verbal span	Thompson et al., 2007; Dittman et al., 2008; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013; Sabater et al., 2016[a]	–	–
Visuospatial span	Fleck et al., 2005[b]; Barrett et al., 2008; Gvirts et al., 2015[c]	–	–

[a] *BD anticonvulsant therapy.*
[b] *Supra span task.*
[c] *Mildly affective symptoms.*

Bipolar Disorder as model for the study of the new component of WM, the Hedonic Detector, for this reason the relationship among WM and other clinical features in the final section.

Cognitive Deficits and Neurobiological Correlates in BD Patients

Regarding the first aim of this review, statistically significant differences in WM performance between groups were found in most studies (Fleck et al., 2005; Thompson et al., 2007; Barrett et al., 2008; Deckersbach et al., 2008; Dittman et al., 2008; Drapier et al., 2008; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013; Pomarol-Clotet et al., 2014; Gvirts et al., 2015; Sabater et al., 2016). These results confirm that BD patients tend to have lower WM performance (MacQueen et al., 2005; Thompson et al., 2007; Lee et al., 2014; Daglas et al., 2015). According to our review both modalities are disrupted, deficits in auditory-verbal information processing were reported in six selected articles (Thompson et al., 2007; Dittman et al., 2008; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013; Sabater et al., 2016) and visuospatial low scores in five other studies (Fleck et al., 2005; Barrett et al., 2008; Drapier et al., 2008; Pomarol-Clotet et al., 2014; Gvirts et al., 2015). Our analysis also showed that the effect sizes of the studies that reported deficit on BD patients on several measures of working memory were small, either on updating or maintenance measures. These effect sizes were 0.33, 0.39, and 0.41, respectively, for updating visuospatial information, processing of visuospatial information, and processing of auditory verbal information. Together with results reported on the papers that showed neurobiological changes of BD patients during the experiments, these results clearly conclude that BD affects both working memory performance and brain functioning.

According to a recent meta-analysis, there is no consensus in the literature defining if cognitive deficits are somatic markers or a consequence of mood episodes in BD (Daglas et al., 2015). Previous researches have shown that information processing, visual episodic memory, and verbal WM deficit were associated with clinical expressions of BD, since it was not observed in first-degree relatives. Therefore, these cognitive lower performances in BD were not associated with genetic susceptibility (Bora et al., 2009). A review by Boland and Alloy (2013) showed that sleep disruption present in BD patients can also be either a predisposing factor or worsening neurocognitive deficits throughout the illness course, resulting in sustained functional deficit, despite the remission of mood symptoms.

Other studies also claimed that the level of neuropsychological deficits in BD was influenced by anti-psychotics and mood stabilizers (Donaldson et al., 2003; Savitz et al., 2008), weakening the hypothesis of WM as a somatic marker of BD. Most studies in the present review used medicated samples, except the article by Roiser et al. (2009) that apparently did this variable. Although, the participants were taking psychotropic medication during assessments, most of the studies of euthymic samples reported significant WM deficits (Thompson et al., 2007; Barrett et al., 2008; Dittman et al., 2008; Drapier et al., 2008; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013). Then, at least in these cases, results do not satisfy the state-independence criterion mentioned by some authors as a key factor in assessing potential endophenotypes of BD (Hasler et al., 2006). Also, the results suggested that WM can be a susceptibility biomarker in BD patients rather than a state-dependent variable of the disorder (Gruber et al., 2009; Kurtz and Gerraty, 2009).

Despite neurobiological correlates of WM are not clearly elucidated in literature, there is evidence of the association between neuropsychological and morphological factors in BD, which support WM deficits as a possible endophenotype of BD (Glahn et al., 2010). Based on 12 studies, a meta-analysis conducted by Lee et al. (2014) showed generalized neuropsychological deficits since the first episode of the disorder. In theory, patients with BD due to the constant changes in both emotional valences; would have an uncalibrated Hedonic Detector. Consequently it would cause deficits in WM as predicted in Baddeley's model (Baddeley, 2007). Besides, in the current review, some studies observed social cognitive deficits affecting emotional response, which is an indirect evidence of dysfunctional Hedonic Detector.

Although, assessing WM deficits in people at high genetic risk of developing BD had not been an objective of this study, it was observed that some authors considered heritability (Drapier et al., 2008; Thermenos et al., 2010; McCormack et al., 2015). Relatives without psychiatric diagnoses did not report significant deficits in WM, but they showed lower scores for verbal reasoning and affective response inhibition (McCormack et al., 2015). In contrast, relatives as BD patients also showed alterations in prefrontal cortex activity and insula during WM task (Drapier et al., 2008; Thermenos et al., 2010). These results show that WM deficits are not only state variables, but seem to be primary character of the disease (Gruber et al., 2009; Kurtz and Gerraty, 2009).

However, based on the reviewed articles there is insufficient data to conclude that WM deficits are present since the onset of disease. Only one study considered population between 18

and 25 years old and it did not show lower WM scores in BD patients (McCormack et al., 2015). Among the eight researches that studied sample aged ranging from 26 to 35 years, three articles showed deficits in WM (Fleck et al., 2005; Gruber et al., 2013; Sabater et al., 2016) and four described neurocognitive deficits in BD patients (Malhi et al., 2007; Deckersbach et al., 2008; Bertocci et al., 2011; Mullin et al., 2012). Ten out of fourteen studies found poor WM performance or other neuropsychological deficits in middle age sample (Thompson et al., 2007; Barrett et al., 2008; Dittman et al., 2008; Drapier et al., 2008; Liu et al., 2010; Thermenos et al., 2010; Levy et al., 2011; Lee et al., 2013; Pomarol-Clotet et al., 2014; Gvirts et al., 2015). There was no study with sample above fifty six years old.

Different Patterns of Cognitive Processes in Each Mood Phase

The second objective of this review was to investigate if diverse BD mood would predict a different WM pattern. Updating deficits of visuospatial information were found in depressive BD patients assessed by n-back tasks (Deckersbach et al., 2008; Pomarol-Clotet et al., 2014) and in mania phases (Pomarol-Clotet et al., 2014). Despite WM alterations have been reported during mood episodes of BD, it is suggested that deficits in WM persist during remission of symptoms (MacQueen et al., 2005; Thompson et al., 2007; Daglas et al., 2015; Farahmand et al., 2015).

According to neurophysiological studies in euthymic phases of BD, patients presented lower prefrontal cortex activation during visuospatial n-back tasks (Malhi et al., 2007; Drapier et al., 2008; Mullin et al., 2012). Mullin et al. (2012), for example, found lower dorsal anterior cingulate cortex (dACC) activity during EFNBACK task with neutral stimuli. In addition, depressive episodes in BD patients showed lower left dorsal anterior midcingulate cortex (dAMCC) activation during visuospatial n-back task with neutral stimuli (Bertocci et al., 2011). In contrast, a different brain activation pattern was reported during n-back tasks with emotional auditory-verbal stimuli. Such as greater left dorsolateral prefrontal cortex (DLPFC) and dACC activation were found when negative valence stimuli were presented (Deckersbach et al., 2008). Therefore, it was suggested that updating was influenced by emotional factors.

According to processing efficiency theory (Eysenck and Calvo, 1992), high levels of anxiety reduce the efficiency of cognitive processing, specifically the central executive of the WM system (Derakshan et al., 2009), confirming the influence of emotions on updating. Besides there are three major control functions of the central executive: inhibition, shifting, and updating (Miyake et al., 2000), study by Eysenck et al. (2007), based on attentional control theory showed that anxiety impairs two major functions of the central executive: negative attentional control (inhibition function) and positive attentional control (shifting function).

In addition, to the decrease activation in dorsolateral prefrontal cortex, parietal alterations in manic, and depressive episodes of BD patients were reported during visuospatial tasks (Pomarol-Clotet et al., 2014). Even in euthymic patients the brain activation pattern varied depending on the mood valences (Malhi et al., 2007). Thus, there was more activity in dACC and amygdala regions over negative valences and a greater connection between dACC and amygdala regions in positive valences (Mullin et al., 2012). It is consistent with the Somatic Marker hypothesis that supports physiological influence on emotional responses through the central executive (Damasio et al., 1991; Damasio, 1998). It was also verified the existence of autonomic changes associated with emotional reactivity during cognitive tasks (Muhtadie and Johnson, 2015). Then, by inference it seems that Hedonic Detector is also affected in WM tasks requiring information updating.

Remarkably, few studies assessed WM performance in more than one mood episode (Fleck et al., 2005; Pomarol-Clotet et al., 2014). Only four papers carried out mood induction prior performing tasks (Malhi et al., 2007; Deckersbach et al., 2008; Bertocci et al., 2011; Mullin et al., 2012) and just the research of autonomic response used a verbal stressor during the test (Muhtadie and Johnson, 2015). In this way, it is difficult to generalize the results for the second objective of this review. In addition, many studies selected BD I patients samples (Fleck et al., 2005; Malhi et al., 2007; Deckersbach et al., 2008; Drapier et al., 2008; Bertocci et al., 2011; Levy et al., 2011; Mullin et al., 2012; Gruber et al., 2013), and few studies assessed BD II subjects. Most papers did not differentiate subtypes of the disorder.

Despite Baddeley's model is the most commonly used theory in WM researches (Malhi et al., 2007; Thompson et al., 2007; Barrett et al., 2008; Dittman et al., 2008; Roiser et al., 2009; Liu et al., 2010; Levy et al., 2011; Gruber et al., 2013; Lee et al., 2013; Miguélez-Pan et al., 2014; Russo et al., 2014; Bauer et al., 2015; Muhtadie and Johnson, 2015), the discrepancies between studies may be explained by the new appearance neuroscience technologies that demand designed tasks such as n-back tasks (Deckersbach et al., 2008; Drapier et al., 2008) to investigate state-based models (D'Esposito, 2007). It appears that authors rarely made the connection between theoretical models and cognitive tasks. Then, despite the fact of some studies confirmed emotion and WM association in depressive or manic BD patients (Malhi et al., 2007; Deckersbach et al., 2008; Mullin et al., 2012; Pomarol-Clotet et al., 2014; Muhtadie and Johnson, 2015), the Hedonic Detector component was not considered in these selected articles of this review.

Once n-back tasks and complex span tasks apparently evaluate different processes (Ribeiro et al., submitted; Kane et al., 2007), WM researches should consider the differences between tasks and how they affect the result explanations (Redick and Lindsey, 2013; Remoli and Santos, 2017). That seems to be crucial for explaining the outcomes and for the replication of future studies (Ribeiro et al., submitted). Further restriction of this review is that diagnoses of BD suffered some changes from DSM-IV (American Psychiatric Association, 2000) to DSM-V (American Psychiatric Association, 2013). This fact could lead some methodological differences in selected studies. However, it

was not the purpose of this work to analyze diagnoses differences of BD.

Relationship among WM and other Clinical Features

Only article by Liu et al. (2010) compared BD I and BD II subjects. They showed that neural activation patterns were different between subgroups of the disorder during auditory-verbal information processing tasks. BD type I patients reported lateralized changes in the right hemisphere and more cognitive deficits while BD type II subjects revealed more distributed lower performance associated with cognitive and emotional processes.

In addition to this other evidence suggest that BD I and II patients present different neuropathological substrates in terms of the loss of bundle coherence or the disruption of fiber tracts (Liu et al., 2010), BD type I and II also exhibit heterogeneous clinical presentations and cognitive functions. Besides BD I patients manifested more cognitive dysfunction in verbal learning, recall, recognition, and set-shifting compared to bipolar II patients (Simonsen et al., 2008), it has been suggested that both suicide and attempted suicide are more common in BD II disorder than in BD I disorder (Jamison, 2000; Rihmer and Kiss, 2002; Hawton et al., 2005).

Article by Levy et al. (2011) showed that BD I patients readmitted to the hospital after 3-month had more psychotic episodes, lower level of global functionality, severe mood episodes, and lower scores for executive function, attention, and WM, visual, and verbal episodic memory performance comparing to outpatients care. While WM low score in BD type I samples were suggested in some studies (Drapier et al., 2008; Levy et al., 2011; Pomarol-Clotet et al., 2014), WM deficits were not found in the majority of BD II sample (Roiser et al., 2009). BD I hospitalized in mania/mixed with psychotic symptoms group also reported lower scores for recognition effectiveness and directed-forgetting effectiveness than expected (Fleck et al., 2005).

Although, epidemiological studies with non-clinical populations have suggested psychotic experiences as a predictor of suicidal behavior (Nishida et al., 2010; DeVylder et al., 2015) and study by Finseth et al. (2012) showed that suicidal attempt are more common in patients with mood disorders with psychotic features, this has not been a consensus in all studies. Besides psychotic symptoms are more common in BD type I patients, a recent study by Gesi et al. (2016) showed that psychotic features, as evaluated upon the presence of delusions or hallucinations, are not associated with suicidality among subjects with BD I, suggesting that suicide behavior is more common in BD type II disorder.

It is important to note that anxiety (Derakshan et al., 2009) and even mood (Derakshan et al., 2009) could modulate cognitive performance as, for example, attentional control. Future studies should address the role of mood states and even positive and negative emotions in working memory in BD patients to explore the role of hedonic detector.

Emotional States and Working Memory: Hedonic Detector and Its Implication to Cognition in Mood Disorders

In fact, the connection between emotional states and working memory plays a role in the measurement instruments and in theoretical framework as well. For instance, the Somatic Marker hypothesis presented by Damasio et al. (1991) describes a mechanism for interaction between emotion and cognition in trial processes and decision-making (Bechara and Damasio, 2002, 2005; Bechara et al., 2005; Verdejo-García and Bechara, 2009). Damasio even states that the executive component of WM could be relevant in this process. Baddeley's model of WM explicitly addressed the interference of emotions in WM information processing, by its new component, the Hedonic Detector (Baddeley, 2007). The Hedonic Detector works as a neutral point that varies between positive and negative valences in response to environmental stimuli. It establishes a mean value between stimulus and information retained in the WM to enable choices of future actions (Baddeley, 2007). In this perspective, improper adjustment of the neutral point could enhance the appearance of pathological affective episodes, for instance, the Bipolar Disorder (BD).

Deficits in WM processing have been consistently reported in euthymic patients (MacQueen et al., 2005; Thompson et al., 2007; Daglas et al., 2015). Another study also observed that euthymic BD type I had worse performance on visuospatial tasks compared to healthy subjects (Farahmand et al., 2015). Although, there is no consensus in the literature, these findings suggest that lower performance in WM could result in the intensification of emotional valences. In other words, the presence of WM deficits, could be considered a primary trace of BD, beyond state variables (Gruber et al., 2009; Kurtz and Gerraty, 2009). However, this particular issue remains controversial due to the diversity of methodologies used across the studies. Apart from the prevalence of within-subjects design, studies rarely made the connection between theoretical models and cognitive tasks, hindering the comprehension about WM components.

In line with this argument, a review by Baddeley (2013) showed that in depressive patients negative mood influences hedonic judgment, explaining the trend of the negative perception of the situations in this clinical population. However, there is no significant evidence in respect to the influence of positive mood in hedonic detection system. Hypothetically, assuming that the neutral point in BD patients corresponds to euthymic phase, the exacerbated positive and negative valences would account for euphoric or depressed mood, respectively (Baddeley, 2007, 2013). As emotion in BD is deregulated, the study of this disorder seems to be necessary to understand the influence of improper adjustment of the Hedonic Detector neutral point in WM.

CONCLUSION

In conclusion, BD mood episodes were associated with both WM processes (updating and serial recall), cognitive lower performance persist even in remission of symptoms. This evidence suggests that BD patients have deficits in monitoring content in WM. But the data at this point is so different across studies that it does not seem prudent to generalize conclusions. Considering that WM deficit apparently is stage-independent in BD patients (Gruber et al., 2009; Kurtz and Gerraty, 2009), future studies should evaluate the convergence of Damasio's Somatic Marker hypotheses and Baddeley's Hedonic Detector in BD. In other words, how the neutral point is deregulated by the interaction between environmental stimuli and mood episodes and affect WM processes.

AUTHOR CONTRIBUTIONS

Conception or design of the work: CS and FS. Data collection: CS. Data analysis and interpretation: CS and FS. Drafting the article: CS, FS, PA, and LM. Critical revision of the article: FS, PA, and LM. Final approval of the version to be published: CS, FS, PA, and LM. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: CS, FS, PA, and LM.

REFERENCES

Ajilore, O., Vizueta, N., Walshaw, P., Zhan, L., Leow, A., and Altshuler, L. L. (2015). Connectome signatures of neurocognitive abnormalities in euthymic bipolar I disorder. *J. Psychiatr. Res.* 68, 37–44. doi: 10.1016/j.jpsychires.2015.05.017

Allen, D. N., Bello, D. T., and Thaler, N. S. (2015). Neurocognitive predictors of performance-based functional capacity in bipolar disorder. *J. Neuropsychol.* 9, 159–171. doi: 10.1111/jnp.12042

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edn.* Washington, DC: American Psychiatric Association.

Arts, B., Jabben, N., Krabbendam, L., and van Os, J. (2009). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives – correction. *Psychol. Med.* 39, 525. doi: 10.1017/S0033291708004972

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Arlington, TX: Springer; American Psychiatric Association.

Baddeley, A. (2013). Working memory and emotion: ruminations on a theory of depression. *Rev. Gen. Psychol.* 17, 20–27. doi: 10.1037/a0030029

Baddeley, A., Banse, R., Huang, Y.-M., and Page, M. (2012). Working memory and emotion: detecting the hedonic detector. *J. Cogn. Psychol.* 24, 6–16. doi: 10.1080/20445911.2011.613820

Baddeley, A. D. (1986). *Working Memory*. Oxford: Clarendon Press.

Baddeley, A. D. (2000). The episodic buffer: a new component of working memory? *Trends Cogn. Sci.* 4, 417–423. doi: 10.1016/S1364-6613(00)01538-2

Baddeley, A. D. (2007). *Working Memory, Thought and Action*. Oxford: Oxford University Press.

Balanzá-Martínez, V., Rubio, C., Selva-Vera, G., Martinez-Aran, A., Sánchez-Moreno, J., Salazar-Fraile, J., et al. (2008). Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: a systematic review. *Neurosci. Biobehav. Rev.* 32, 1426–1438. doi: 10.1016/j.neubiorev.2008.05.019

Barrett, S. L., Kelly, C., Bell, R., and King, D. J. (2008). Gender influences the detection of spatial working memory deficits in bipolar disorder. *Bipolar Disord.* 10, 647–654. doi: 10.1111/j.1399-5618.2008.00592.x

Bauer, I. E., Keefe, R. S. E., Sanches, M., Suchting, R., Green, C. E., and Soares, J. C. (2015). Evaluation of cognitive function in bipolar disorder using the Brief Assessment of Cognition in Affective Disorders (BAC-A). *J. Psychiatr. Res.* 60, 81–86. doi: 10.1016/j.jpsychires.2014.10.002

Bechara, A., and Damasio, A. R. (2005). The somatic marker hypothesis: a neural theory of economic decision. *Games Econ. Behav.* 52, 336–372. doi: 10.1016/j.geb.2004.06.010

Bechara, A., and Damasio, H. (2002). Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia* 40, 1675–1689. doi: 10.1016/S0028-3932(02)00015-5

Bechara, A., Damasio, H., Tranel, D., and Damasio, A. R. (2005). The Iowa Gambling task and the somatic marker hypothesis: some questions and answers. *Trends Cogn. Sci.* 9, 159–162. doi: 10.1016/j.tics.2005.02.002

Bento, T. (2014). Revisões sistemáticas em desporto e saúde: orientações para o planeamento, elaboração, redação e avaliação. *Motricidade* 10, 107–123. doi: 10.6063/motricidade.10(2).3699

Bertocci, M. A., Bebko, G. M., Mullin, B. C., Langenecker, S. A., Ladouceur, C. D., Almeida, J. R. C., et al. (2011). Abnormal anterior cingulate cortical activity during emotional n-back task performance distinguishes bipolar from unipolar depressed females. *Psychol. Med.* 42, 1417–1428. doi: 10.1017/S003329171100242X

Boland, E. M., and Alloy, L. B. (2013). Sleep disturbance and cognitive deficits in bipolar disorder: toward an integrated examination of disorder maintenance and functional impairment. *Clin. Psychol. Rev.* 33, 33–44. doi: 10.1016/j.cpr.2012.10.001

Bora, E., Bartholomeusz, C., and Pantelis, C. (2016). Meta-analysis of Theory of Mind (ToM) impairment in bipolar disorder. *Psychol. Med.* 46, 253–264. doi: 10.1017/S0033291715001993

Bora, E., Yucel, M., and Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J. Affect. Disord.* 113, 1–20. doi: 10.1016/j.jad.2008.06.009

Bora, E., Yücel, M., Pantelis, C., and Berk, M. (2011). Meta-analytic review of neurocognition in bipolar II disorder. *Acta Psychiatr. Scand.* 123, 165–174. doi: 10.1111/j.1600-0447.2010.01638.x

Chang, Y.-H., Chen, S.-L., Lee, S.-Y., Hsu, Y.-W., Wu, J. Y.-W., Chen, S.-H., et al. (2012). Neuropsychological functions in bipolar disorders I and II with and without comorbid alcohol dependence. *Prog. Neuro Psychopharmacol. Biol. Psychiatry* 37, 211–216. doi: 10.1016/j.pnpbp.2012.01.015

Clark, L., Iversen, S. D., and Goodwin, G. M. (2001). A neuropsychological investigation of prefrontal cortex involvement in acute mania. *Am. J. Psychiatry* 158, 1605–1611. doi: 10.1176/appi.ajp.158.10.1605

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences, 2nd Edn*. Hillsdale, NJ: Lawrence Erbaum.

Conway, A. R. A., and Kovacs, K. (2013). Individual differences in intelligence and working memory. *Psychol. Learn. Motiv.* 233–270. doi: 10.1016/B978-0-12-407237-4.00007-4

Cullen, B., Ward, J., Graham, N. A., Deary, I. J., Pell, J. P., Smith, D. J., et al. (2016). Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: a systematic review. *J. Affect. Disord.* 205, 165–181. doi: 10.1016/j.jad.2016.06.063

Daglas, R., Yücel, M., Cotton, S., Allott, K., Hetrick, S., and Berk, M. (2015). Cognitive impairment in first-episode mania: a systematic review of the evidence in the acute and remission phases of the illness. *Int. J. Bipolar Disord.* 3:9. doi: 10.1186/s40345-015-0024-2

Damasio, A. R. (1998). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Prefrontal Cortex Exec. Cogn. Funct.* 351, 36–50. doi: 10.1093/acprof:oso/9780198524410.003.0004

Damasio, A. R., Tranel, D., and Damasio, H. (1991). "Somatic markers and the guidance of behaviour: theory and preliminary testing," in *Frontal Lobe Function and Dysfunction*, eds H. S. Levin, H. M. Eisenberg, and A. L. Benton (New York, NY: Oxford University Press), 217–229.

Daneman, M., and Merikle, P. M. (1996). Working memory and language comprehension: a meta-analysis. *Psychon. Bull. Rev.* 3, 422–433. doi: 10.3758/BF03214546

Deckersbach, T., Rauch, S. L., Buhlmann, U., Ostacher, M. J., Beucke, J.-C., Nierenberg, A. A., et al. (2008). An fMRI investigation of working memory and sadness in females with bipolar disorder: a brief report. *Bipolar Disord.* 10, 928–942. doi: 10.1111/j.1399-5618.2008.00633.x

Derakshan, N., Smyth, S., and Eysenck, M. W. (2009). Effects of state anxiety on performance using a task-switching paradigm: an investigation of attentional control theory. *Psychon. Bull. Rev.* 16, 1112–1117. doi: 10.3758/PBR.16.6.1112

D'Esposito, M. (2007). From cognitive to neural models of working memory. *Philos. Trans. R. Soc. B.* 362, 761–772. doi: 10.1098/rstb.2007.2086

DeVylder, J. E., Thompson, E., Reeves, G., and Schiffman, J. (2015). Psychotic experiences as indicators of suicidal ideation in a non-clinical college sample. *Psychiatry Res.* 226, 489–493. doi: 10.1016/j.psychres.2015.02.007

Dittman, S., Seemuller, F., Grunze, H. C., Schwarz, M. J., Zach, J., Fast, K., et al. (2008). The impact of homocysteine levels on cognition in euthymic bipolar patients. *J. Clin. Psychiatry* 69, 899–906. doi: 10.4088/JCP.v69n0603

Donaldson, S., Goldstein, L. H., Landau, S., Raymont, V., and Frangou, S. (2003). The maudsley bipolar disorder project. *J. Clin. Psychiatry* 64, 86–93. doi: 10.4088/JCP.v64n0116

Drapier, D., Surguladze, S., Marshall, N., Schulze, K., Fern, A., Hall, M.-H., et al. (2008). Genetic liability for bipolar disorder is characterized by excess frontal activation in response to a working memory task. *Biol. Psychiatry* 64, 513–520. doi: 10.1016/j.biopsych.2008.04.038

Eysenck, M. W., and Calvo, M. G. (1992). Anxiety and performance: the processing efficiency theory. *Cogn. Emot.* 6, 409–434. doi: 10.1080/02699939208409696

Eysenck, M. W., Derakshan, N., Santos, R., and Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion* 7, 336–353. doi: 10.1037/1528-3542.7.2.336

Farahmand, Z., Tehrani-Doost, M., Amini, H., Mohammadi, A., Mirzaei, M., and Mohamadzadeh, A. (2015). Working memory and response inhibition in patients with bipolar I disorder during euthymic period. *Iran. J. Psychiatry Behav. Sci.* 9:e209. doi: 10.17795/ijpbs209

Finseth, P. I., Morken, G., Andreassen, O. A., Malt, U. F., and Vaaler, A. E. (2012). Risk factors related to lifetime suicide attempts in acutely admitted bipolar disorder inpatients. *Bipolar Disord.* 14, 727–734. doi: 10.1111/bdi.12004

Fleck, D. E., Shear, P. K., and Strakowski, S. M. (2005). Processing efficiency and directed forgetting in bipolar disorder. *J. Int. Neuropsychol. Soc.* 11, 871–880. doi: 10.1017/s1355617705051027

Gesi, C., Carmassi, C., Miniati, M., Benvenuti, A., Massimetti, G., and Dell'Osso, L. (2016). Psychotic spectrum symptoms across the lifespan are related to lifetime suicidality among 147 patients with bipolar I or major depressive disorder. *Ann. Gen. Psychiatry* 15:15. doi: 10.1186/s12991-016-0101-7

Glahn, D. C., Almasy, L., Barguil, M., Hare, E., Peralta, J. M., Kent, J. W., et al. (2010). Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Arch. Gen. Psychiatry* 67, 168. doi: 10.1001/archgenpsychiatry.2009.184

Gruber, J., Purcell, A. L., Perna, M. J., and Mikels, J. A. (2013). Letting go of the bad: deficit in maintaining negative, but not positive, emotion in bipolar disorder. *Emotion* 13, 168–175. doi: 10.1037/a0029381

Gruber, O., Tost, H., Henseler, I., Schmael, C., Scherk, H., Ende, G., et al. (2009). Pathological amygdala activation during working memory performance: evidence for a pathophysiological trait marker in bipolar affective disorder. *Hum. Brain Mapp.* 31, 115–125 doi: 10.1002/hbm.20849

Gvirts, H. Z., Braw, Y., Harari, H., Lozin, M., Bloch, Y., Fefer, K., et al. (2015). Executive dysfunction in bipolar disorder and borderline personality disorder. *Euro. Psychiatry* 30, 959–964. doi: 10.1016/j.eurpsy.2014.12.009

Hasler, G., Drevets, W. C., Gould, T. D., Gottesman, I. I., and Manji, H. K. (2006). Toward constructing an endophenotype strategy for bipolar disorders. *Biol. Psychiatry* 60, 93–105. doi: 10.1016/j.biopsych.2005.11.006

Hawton, K., Sutton, L., Haw, C., Sinclair, J., and Harriss, L. (2005). Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J. Clin. Psychiatry* 66, 693–704.

Higgins, J. P. T., and Green, S. (eds.). (2011). *Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, 2011*, Version 5. 1. 0. Available online at: http://handbook.cochrane.org

Jamison, K. R. (2000). Suicide and bipolar disorder. *J. Clin. Psychiatry* 61(Suppl. 9), 47–51.

Kane, M. J., Conway, A. R. A., Hambrick, D. Z., and Engle, R. W. (2008). Variation in working memory capacity as variation in executive attention and control. *Variation Work. Mem.* 1, 21–48. doi: 10.1093/acprof:oso/9780195168648.003.0002

Kane, M. J., Conway, A. R., Miura, T. K., and Colflesh, G. J. H. (2007). Working memory, attention control, and the n-back task: a question of construct validity. *J. Exp. Psychol. Learn. Mem. Cogn.* 33, 615–622. doi: 10.1037/0278-7393.33.3.615

Kurtz, M. M., and Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology* 23, 551–562. doi: 10.1037/a0016277

Lage, G. M., Malloy-Diniz, L. F., Neves, F. S., Gallo, L. G., Valentini, A. S., and Corrêa, H. (2013). A kinematic analysis of manual aiming control on euthymic bipolar disorder. *Psychiatry Res.* 208, 140–144. doi: 10.1016/j.psychres.2012.09.046

Latalova, K., Prasko, J., Diveky, T., and Velartova, H. (2011). Cognitive impairment in bipolar disorder. *Biomed. Papers* 155, 19–26. doi: 10.5507/bp.155.2011.003

LeDoux, J. E. (2000). Emotion circuits in the brain. *Ann. Rev. Neurosci.* 23, 155–184. doi: 10.1146/annurev.neuro.23.1.155

Lee, J., Altshuler, L., Glahn, D. C., Miklowitz, D. J., Ochsner, K., and Green, M. F. (2013). Social and nonsocial cognition in bipolar disorder and schizophrenia: relative levels of impairment. *Am. J. Psychiatry* 170, 334–341. doi: 10.1176/appi.ajp.2012.12040490

Lee, R. S., Hermens, D. F., Scott, J., Redoblado-Hodge, M. A., Naismith, S. L., Lagopoulos, J., et al. (2014). A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. *J. Psychiatr. Res.* 57, 1–11. doi: 10.1016/j.jpsychires.2014.06.019

Levy, B., Medina, A. M., Manove, E., and Weiss, R. D. (2011). The characteristics of a discrete mood episode, neuro-cognitive impairment and re-hospitalization in bipolar disorder. *J. Psychiatr. Res.* 45, 1048–1054. doi: 10.1016/j.jpsychires.2011.01.005

Lima, M., Tassi, J., Novo, I., and Mari, J. (2005). Epidemiologia do transtorno bipolar. *Arch. Clin. Psychiatry*32, 15–20. doi: 10.1590/s0101-60832005000700003

Liu, J.-X., Chen, Y.-S., Hsieh, J.-C., Su, T.-P., Yeh, T.-C., and Chen, L.-F. (2010). Differences in white matter abnormalities between bipolar I and II disorders. *J. Affect. Disord.* 127, 309–315. doi: 10.1016/j.jad.2010.05.026

Loschiavo, F., Sedyiama, C. Y., Neves, F. S., Corrêa, H., Malloy-Diniz, L., and Bateman, A. (2013). Clinical application of DEX-R for patients with bipolar disorder type I and II. *Clin. Neuropsychiatry* 10, 86–94.

MacQueen, G. M., Hajek, T., and Alda, M. (2005). The phenotypes of bipolar disorder: relevance for genetic investigations. *Mol. Psychiatry* 10, 811–826. doi: 10.1038/sj.mp.4001701

Malhi, G. S., Lagopoulos, J., Owen, A. M., Ivanovski, B., Shnier, R., and Sachdev, P. (2007). Reduced activation to implicit affect induction in euthymic bipolar patients: an fMRI study. *J. Affect. Disord.* 97, 109–122. doi: 10.1016/j.jad.2006.06.005

Mann-Wrobel, M. C., Carreno, J. T., and Dickinson, D. (2011). Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. *Bipolar Disord.* 13, 334–342. doi: 10.1111/j.1399-5618.2011.00935.x

Martinez-Aran, A., Vieta, E., Torrent, C., Sanchez-Moreno, J., Goikolea, J., Salamero, M., et al. (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disord.* 9, 103–113. doi: 10.1111/j.1399-5618.2007.00327.x

McCormack, C., Green, M. J., Rowland, J. E., Roberts, G., Frankland, A., Hadzi-Pavlovic, D., et al. (2015). Neuropsychological and social cognitive function in young people at genetic risk of bipolar disorder. *Psychol. Med.* 46, 745–758. doi: 10.1017/S0033291715002147

McKenna, B. S., Sutherland, A. N., Legenkaya, A. P., and Eyler, L. T. (2013). Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder. *Bipolar Disord.* 16, 289–299. doi: 10.1111/bdi.12126

Miguélez-Pan, M., Pousa, E., Cobo, J., and Duño, R. (2014). Cognitive executive performance influences functional outcome in euthymic type I bipolar disorderoutpatients. *Psicothema* 26, 166–173. doi: 10.7334/psicothema2013.111

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Miyake, A., and Shah, P. (eds.). (1999). *Models of Working Memory: Mechanisms of Active Maintenance and Executive Control, 1st Edn.* New York, NY: Cambridge University Press.

Muhtadie, L., and Johnson, S. L. (2015). Threat sensitivity in bipolar disorder. *J. Abnorm. Psychol.* 124, 93–101. doi: 10.1037/a0038065

Mullin, B. C., Perlman, S. B., Versace, A., de Almeida, J. R. C., LaBarbara, E. J., Klein, C., et al. (2012). An fMRI study of attentional control in the context of emotional distracters in euthymic adults with bipolar disorder. *Psychiatry Res.* 201, 196–205. doi: 10.1016/j.pscychresns.2011.09.002

Murphy, F. C. (2001). Neuropsychology of bipolar disorder. *Br. J. Psychiatry* 178, 120s–127s. doi: 10.1192/bjp.178.41.s120

National Institute of Mental Health (2011). *Fact Sheeton Bipolar Disorder.* Available online at: https://www.nimh.nih.gov/health/statistics/prevalence/bipolar-disorder-among-adults.shtml (Accessed February 15, 2016).

Neves, M. C., Albuquerque, M. R., Neves, F. S., Lage, G. M., Malloy-Diniz, L., Nicolato, R., et al. (2014). Sensorimotor performance in euthymic bipolar disorder: the MPraxis (PennCNP) analysis. *Rev. Bras. Psiquiatr.* 36, 248–250. doi: 10.1590/1516-4446-2013-1243

Nishida, A., Sasaki, T., Nishimura, Y., Tanii, H., Hara, N., Inoue, K., et al. (2010). Psychotic-like experiences are associated with suicidal feelings and deliberate self-harm behaviors in adolescents aged 12–15 years. *Acta Psychiatr. Scand.* 121, 301–307. doi: 10.1111/j.1600-0447.2009.01439.x

Pomarol-Clotet, E., Alonso-Lana, S., Moro, N., Sarro, S., Bonnin, M. C., Goikolea, J. M., et al. (2014). Brain functional changes across the different phases of bipolar disorder. *Br. J. Psychiatry* 206, 136–144. doi: 10.1192/bjp.bp.114.152033

Raucher-Chéné, D., Achim, A. M., Kaladjian, A., and Besche-Richard, C. (2017). Verbal fluency in bipolar disorders: a systematic review and meta-analysis. *J. Affect. Disord.* 207, 359–366. doi: 10.1016/j.jad.2016.09.039

Redick, T. S., and Lindsey, D. R. B. (2013). Complex span and n-back measures of working memory: a meta-analysis. *Psychon. Bull. Rev.* 20, 1102–1113. doi: 10.3758/s13423-013-0453-9

Remoli, T. C., and Santos, F. H. (2017). Interactions between working memory and creativity: a systematic review. *Psicol. Estud.* 22, 53–65. doi: 10.4025/psicolestud.v22i1.32518

Rihmer, Z., and Kiss, K. (2002). Bipolar disorder and suicidal behavior. *Bipolar Disord.* 4(Suppl 1), 21–25. doi: 10.1034/j.1399-5618.4.s1.3.x

Robinson, L. J., Thompson, J. M., Gallagher, P., Goswami, U., Young, A. H., Ferrier, I. N., et al. (2006). A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J. Affect. Disord.* 93, 105–115. doi: 10.1016/j.jad.2006.02.016

Roiser, J. P., Cannon, D. M., Gandhi, S. K., Tavares, J. T., Erickson, K., Wood, S., et al. (2009). Hot and cold cognition in unmedicated depressed subjects with bipolar disorder. *Bipolar Disord.* 11, 178–189. doi: 10.1111/j.1399-5618.2009.00669.x

Rubinsztein, J. S., Michael, A., Paykel, E. S., and Sahakian, B. J. (2000). Cognitive impairment in remission in bipolar affective disorder. *Psychol. Med.* 30, 1025–1036. doi: 10.1017/S0033291799002664

Russo, M., Mahon, K., Shanahan, M., Ramjas, E., Solon, C., Braga, R. J., et al. (2014). Affective temperaments and neurocognitive functioning in bipolar disorder. *J. Affect. Disord.* 169, 51–56. doi: 10.1016/j.jad.2014.07.038

Sabater, A., García-Blanco, A. C., Verdet, H. M., Sierra, P., Ribes, J., Villar, I., et al. (2016). Comparative neurocognitive effects of lithium and anticonvulsants in long-term stable bipolar patients. *J. Affect. Disord.* 190, 34–40. doi: 10.1016/j.jad.2015.10.008

Samamé, C., Martino, D. J., and Strejilevich, S. A. (2015). An individual task meta-analysis of social cognition in euthymic bipolar disorders. *J. Affect. Disord.* 173, 146–153. doi: 10.1016/j.jad.2014.10.055

Santos, F. H., Soares, R. F. G., and Albuquerque, P. B. (2015). "How emotions modulate working memory capacity?," in *Poster Presented at the 19th Conference of the European Society for Cognitive Psychology* (Paphos: ESCOP).

Savitz, J. B., van der Merwe, L., Stein, D. J., Solms, M., and Ramesar, R. S. (2008). Neuropsychological task performance in bipolar spectrum illness: genetics, alcohol abuse, medication and childhood trauma. *Bipolar Disord.* 10, 479–494. doi: 10.1111/j.1399-5618.2008.00591.x

Simonsen, C., Sundet, K., Vaskinn, A., Birkenaes, A. B., Engh, J. A., Hansen, C. F., et al. (2008). Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. *Bipolar Disord.* 10, 245–255. doi: 10.1111/j.1399-5618.2007.00492.x

Soares, R. F. G. (2015). *Influência da Indução de Emoções Positivas e Negativas na Memória Operatória*. Braga: Universidade do Minho.

Spachtholz, P., Kuhbandner, C., and Pekrun, R. (2014). Negative affect improves the quality of memories: trading capacity for precision in sensory and working memory. *J. Exp. Psychol.* 143, 1450–1456. doi: 10.1037/xge0000012

Spies, K., Heese, F. W., and Hunimitzsch, C. (1996). Mood and capacity in Baddeley's model of human memory. *Z. Psychol.* 204, 367–381.

St Clair-Thompson, H. L., and Gathercole, S. E. (2006). Executive functions and achievements in school: shifting, updating, inhibition, and working memory. *Q. J. Exp. Psychol.* 59, 745–759. doi: 10.1080/17470210500162854

Sweeney, J. A., Kmiec, J. A., and Kupfer, D. J. (2000). Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. *Biol. Psychiatry* 48, 674–684. doi: 10.1016/S0006-3223(00)00910-0

Thermenos, H. W., Goldstein, J. M., Milanovic, S. M., Whitfield-Gabrieli, S., Makris, N., LaViolette, P., et al. (2010). An fMRI study of working memory in persons with bipolar disorder or at genetic risk for bipolar disorder. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* 153B, 120–131. doi: 10.1002/ajmg.b.30964

Thompson, J. M., Gray, J. M., Hughes, J. H., Watson, S., Young, A. H., and Nicol Ferrier, I. (2007). Impaired working memory monitoring in euthymic bipolar patients. *Bipolar Disord.* 9, 478–489. doi: 10.1111/j.1399-5618.2007.00470.x

Torres, I. J., Boudreau, V. G., and Yatham, L. N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr. Scand.* 116, 17–26. doi: 10.1111/j.1600-0447.2007.01055.x

Unsworth, N., and Engle, R. W. (2007). The nature of individual differences in working memory capacity: active maintenance in primary memory and controlled search from secondary memory. *Psychol. Rev.* 114, 104–132. doi: 10.1037/0033-295X.114.1.104

van Gorp, W. G., Altshuler, L., Theberge, D. C., Wilkins, J., and Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. *Arch. Gen. Psychiatry* 55:41. doi: 10.1001/archpsyc.55.1.41

Verdejo-García, A., and Bechara, A. (2009). A somatic-marker theory of addiction. *Neuropharmacology* 56(Suppl. 1), 48–62. doi: 10.1016/j.neuropharm.2008.07.035

Wilhelm, O., Hildebrandt, A., and Oberauer, K. (2013). What is working memory capacity, and how can we measure it? *Front. Psychol.* 4:433. doi: 10.3389/fpsyg.2013.00433

Wingo, A. P., Harvey, P. D., and Baldessarini, R. J. (2009). Neurocognitive impairment in bipolar disorder patients: functional implications. *Bipolar Disord.* 11, 113–125. doi: 10.1111/j.1399-5618.2009.00665.x

World Health Organization (2016). *Regional Office for Europe.* Available online at: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/data-and-statistics (Accessed November 7, 2016).

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Executive Function Is Selectively Impaired in Old Age Bipolar Depression

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Background: Little is known about the cognitive signature of bipolar disorder (BD) in elderly brains. The neuropsychological features of depressive elderly with early-onset BD are largely unknown. This issue is relevant because cognitive impairment can produce an additional impact on the already compromised functionality of elderly with BD. The aim of this study is to assess executive functions (EFs) in the depressive phase of elderly outpatients with early-onset BD.

Methods: Forty-nine elderly outpatients with early-onset BD were assessed with several neuropsychological tests for EF in the depressive phase of the disorder.

Results: Executive dysfunction is very common in old age bipolar depression. Thirteen patients (26.5%) had a pseudodementia presentation. The worst performances were observed in the following tests: Trail Making B, Stroop Test 3, Backward Digit Span and Wisconsin Card Sorting Test.

Conclusion: Executive dysfunction profile in elderly BD is complex and heterogeneous, but most cases display difficulties in working memory, inhibitory control, mental flexibility, and information processing speed. The performance of elderly with bipolar depression in executive assessment can be divided into two main categories: (1) Single EF domain impairment; and (2) Multiple EF domain impairment with or without a pseudodementia syndrome. Executive dysfunction in old age bipolar depression may be explained by lack of sufficient mental energy to run those cognitive processes that require larger amounts of effort to be performed.

Keywords: aging, bipolar disorder, elderly patients, executive dysfunctions, neuropsychology

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INTRODUCTION

Bipolar disorder (BD) in the elderly is a growing public health concern and a major cause of disability (Sajatovic et al., 2015). Despite considerable knowledge accumulated in recent decades points to the presence of cognitive impairment in BD (Tsitsipa and Fountoulakis, 2015), few consistent data exist on the neuropsychology of old age patients with BD. Studies with very selective samples and multiple age groups suggest that higher age in BD is associated with greater neurocognitive deficits (Kessler et al., 2013). Some authors state that elderly patients with BD have significant cognitive disabilities and that BD with late onset is associated with more severe cognitive impairment than early-onset BD (Schouws et al., 2007, 2009),

but all these studies were done in euthymic BD. There is a lack of knowledge especially in relation to the neuropsychology of bipolar depression in late life (Rise et al., 2016).

Little is known about the cognitive signature of BD in elderly brains. This issue is relevant because cognitive impairment can produce an additional impact on the already compromised functionality of elderly with BD (Rise et al., 2016). Besides that, the identification of specific cognitive profiles in BD can perhaps help differentiate subgroups and pave the way to the identification of possible endophenotypes (Volkert et al., 2016). Finally, a comprehensive mapping of cognitive domains impaired in BD can add some insights into the physiopathology of the disorder and the many mechanisms by which cognitive symptoms may relate to behavior alterations. For instance, in the young adult it is known that cognitive deficits in BD are directly related to the daily losses presented by these patients in social adaptation or even in suicide behavior (Malloy-Diniz et al., 2009).

Among the most disputed issues in contemporary cognitive neuropsychiatry is the deterioration of executive functions (EF) and the neurocircuitry disruption that support these disabilities. EFs impact affective-emotional, motivational, and social skills. Executive dysfunction may represent an important contributor to the cognitive, functional and social impairments usually observed in adults (Tsitsipa and Fountoulakis, 2015) and elderly (Schouws et al., 2009) with BD.

The aim of this study is to assess EFs in the depressive phase of elderly outpatients with early-onset BD.

MATERIALS AND METHODS

Participants

We have selected 49 consecutive elderly outpatients diagnosed by the same senior psychiatrist (LC) as a BD according to DSM-5 criteria, from the BD program in a university hospital (Hospital das Clínicas at the Federal University of Goiás) in Central Brazil, from August 2013 to 2015. All subjects provided written informed consent, as required by the ethical committee of Federal University of Goiás. The hospital's catchment area involves a population of approximately 1500 elderly. We calculated a sample size of 50.33 patients with a sampling error of approximately 2.13% at a 95% confidence level. Originally, 157 elderly bipolar patients were enrolled in the service. Of these, 91 were eliminated by the exclusion criteria (44 patients with late-onset BD – type VI; 42 with dementia; 3 alcoholics; and 2 with psychostimulant use). Thus, 66 patients were eligible for the study, but 17 refused or could not undergo neuropsychological evaluation, leaving, therefore, 49 patients to compose the definitive sample.

Inclusion criteria were: age 60–90 years old; the onset of BD prior to the age of 40 years (definition of 'early-onset' BD [Schouws et al., 2009]); any ethnicity; portuguese speaking Brazilian outpatients; followed at least during 1 year in our service with serial (monthly) psychiatric assessment in order to rule out primary dementia cases. We have included any degree of cognitive and functional impairment. We have excluded from our search elderly bipolar patients who began their disease late in life (BD type VI), since this subtype has a strong association with neurological disease and structural damage to the brain (Ng et al., 2008), what could interfere in the neuropsychological performance. The same senior psychiatrist (LC) made the diagnosis of BD and assessed the diagnosis for the depressive phase of BD.

According to international recommendations (Burdick et al., 2015), it was excluded subjects taking high-dose anticholinergics, topiramate, clozapine, tricyclics, benzodiazepines, psychostimulants, and those who had electroconvulsivetherapy within past 6 months. Medication titration could not be done in the week of neuropsychological assessment. Patients with general clinical conditions which could impact cognitive performance were also not included in our sample: delirium, untreated hypothyroidism, severe anemia, AIDS, any kind of encephalopathy.

Laboratory Testing and Neuroimaging

All patients were submitted to laboratory screening and neuroimaging exams according international recommendations (Knopman et al., 2001) in order to rule out systemic or neurological causes of cognitive impairment and primary dementias with structural brain damage.

Neuropsychological Assessment

Neuropsychological assessment of the patients was carried out by three senior clinical neuropsychologists (VLDS, CDS, SBF).

Patients were evaluated during the depressive phase. Total assessment was divided into three sessions of 30 min each within a period of 3 days in order to prevent mental fatigue. All patients were submitted to the most frequently used tests for assessing EFs in aging (Faria et al., 2015), consisting of subtests from standard test batteries validated for Portuguese use in Brazilian patients: (1) Trail Making Test Form A (TMT-A): attention, information processing speed; (2) Trail Making Test Form B (TMT-B): mental flexibility, information processing speed; (3) Stroop Test: inhibitory control; (4) Digits Forward and Backward subtests (WAIS-R): working memory; (5) Wisconsin Card Sorting Test (WCST): mental flexibility; (6) Verbal Fluency Test (Animals category): verbal fluency and information processing speed; (7) Verbal Fluency or Letter Fluency Test – FAS: verbal fluency, information processing speed and active search for specific information in memory.

Statistical Analysis

Clinical data were statistically analyzed using conventional descriptive methods. Quantitative variables were described as means and standard deviations, while categorical variables were described using frequency and percentages.

When describing neuropsychological performance in depressive bipolar elderly, we transformed raw scores for all individual neuropsychological tests (except WCST) into *Z*-scores using the distribution of the older adult controls' database (i.e., controls' performance on any test has mean of 0 and SD of 1). For WCST was used *T*-score; scores were considered abnormal based on Brazilian norms and validation of these instruments in Brazilian population (Zimmermann et al., 2015).

RESULTS

The mean age of BD patients was 69.1 years (60–88, ±7.0). Most patients were female ($n = 31$; 62.2%). The mean schooling was 10.8 years (±4.2).

Table 1 shows the descriptive analysis (mean, standard deviation) of the neuropsychological assessment.

Of patients, 28 (57.1%) scored −2SDs (moderate impairment) on at least one EF test measure, and 49 (100%) scored lowest than −1SD on at least one EF test measure or, in other words, none of the patients had a normal performance in all EF tests.

Forty patients (81.6% of total sample) presented a more extensive and severe dysexecutive profile, involving many EFs. From these, thirteen patients (26.5%) had a pseudodementia presentation.

Nine patients (18.3%) had a mild executive dysfunction (affecting, for example, only one executive domain, such as working memory or mental flexibility).

The mean of WCST (24.4) according *T*-score is in the diagnostic category of "moderately-to-severely impaired range" (Heaton et al., 1993). No patient was able to complete all categories of WCST perfectly.

Twenty-three patients (46.9%) had scores lowest than −1SD on VFT-animals and 22 (44.8%) on FAS. On average, patients had difficulty in verbal fluency tasks as indicated by negative *Z*-scores, but the mean does not exceed the adopted *Z*-score cutoff. On average, performance on VFT (Animals category) was worse than FAS (−0.86 versus −0.69, respectively).

DISCUSSION

Our data support the notion that executive dysfunction is very common in elderly with BD, since all the sample had performance below average in at least one EF test. Moreover, we report new data concerning executive dysfunction in BD elderly outpatients in the depressive phase, since studies are focused on euthymic or manic elderly (Young et al., 2006; Schouws et al., 2007, 2009; Samamé et al., 2013). It is not clear whether bipolar and unipolar old age depression have similar or different cognitive profiles, but our data, when compared to the cognitive profile described in the literature for unipolar depression in the elderly (Dybedal et al., 2013; Pantzar et al., 2014), show similarity in executive dysfunction between both forms of depression. Xu et al. (2012) studying adults state that bipolar and unipolar patients have a similar pattern of cognitive impairment during the state of acute depressive episode.

It is remarkably difficult to make definite statements about the neuropsychology of BD, since it depends on the BD type, age considered, medications in use, and mood state at the time of neuropsychological assessment (Tsitsipa and Fountoulakis, 2015). Even in a relatively homogeneous sample as ours, in which we have specifically arranged elderly, BD patients, in the depressive phase, the cognitive profile is not uniform. Notwithstanding all the sample presented with some degree of executive dysfunction, it was found a large span of executive performance among subjects, as indicated by the high variability between minimum and maximum scores, and varying from mild executive dysfunction (affecting, for example, only one executive domain, such as selective attention or working memory), until a more extensive and severe dysexecutive profile (involving many EFs, such as mental flexibility, mental engagement, self-control, self-monitoring, many attention domains and working memory). Therefore, BD elderly patients can indeed reach a level of cognitive dysfunction in their depressive phase compatible with a dementia syndrome (depressive pseudodementia). Based on our data, we can divide patients' performance in neuropsychological assessment into two main categories: (1) Single EF domain impairment; and (2) Multiple EF domain impairment. The

TABLE 1 | Statistical description of executive function tests in elderly with bipolar depression ($n = 49$).

Tests	Minimum	Maximum	Mean	Standard deviation
Stroop Test 1	−6.05	6.24	1.17	2.30
Stroop Test 2	−0.02	7.52	2.02	2.01
Stroop Test 3	−5.19	1.55	−1.05	1.42
Errors Stroop 1	0	1.00	0.04	0.20
Errors Stroop 2	0	6.00	0.23	0.98
Errors Stroop 3	0	15.00	1.79	3.17
TMT-A	−8.08	8.05	1.30	3.38
TMT-A errors	0	4.00	0.19	0.77
TMT-B	−10.44	1.06	−2.02	2.40
TMT-B errors	0	26.00	8.84	8.44
VF Digit Span	−1.85	1.34	−0.55	0.48
VB Digit Span	−2.54	0.10	−1.17	0.55
VFT – Animals category	−2.39	1.66	−0.86	0.81
VFT – FAS	−2.31	1.89	−0.69	1.00
WCST	15	49.00	24.42	9.27

TMT, Trail Making Test; VF Digit Span, Visual Forward Digit Span; VB Digit Span, Visual Backward Digit Span; VFT, Verbal Fluency Test; WCST, Wisconsin Card Sorting Test. For all tests (except WCST) was used Z-score. For WCST was used T-score.

second one can present with or without a pseudodementia syndrome.

One of the most impaired functions in the elderly with BD in our sample was mental flexibility, assessed by TMT-B and WCST. These two tests also recruit working memory, selective attention, mental engagement and are sensitive to impulsive behavior (Faria et al., 2015). As these functions are related to the dorsolateral prefrontal areas in the brain, we can assume that in depressive phase of BD elderly the neural circuits involving this topography are somewhat affected. In fact, some authors (Brooks et al., 2010) have found dorsolateral prefrontal hypometabolism using positron emission tomography associated with impaired performance on executive tasks among older adults with BD.

Inhibitory control is a core member of the EFs and generally refers to the capacity to actively inhibit or delay a dominant response to achieve a goal. Inhibitory control is impaired in BD elderly as showed by poor performance in Stroop Test 3 seen in our sample. The ability to inhibit an automatic behavior and perform a controlled behavior is associated to ventral-fronto-striatal circuitry (Durston et al., 2002), therefore we can suggest that this network is somewhat impaired in the depressive phase of BD. Penfold et al. (2015) also found inferior prefrontal hypoactivation (using MRI) in medication-free adults with bipolar depression during response inhibition test. The weakening of inhibitory control can contribute to some aspects of social and functional impairment seen in BD, and can explain in part how depressive BD meet the day-to-day demands of conflict, delay, and compliance challenges.

Information processing speed is impaired in our sample of old age bipolar depression as suggested by TMT-B poor performances. Processing speed was also one of the most impaired cognitive functions in many studies dealing with BD in adults (Xu et al., 2012; Kessler et al., 2013). In fact, some authors (Volkert et al., 2016) suggest that reduced psychomotor speed could serve as a potential endophenotype for BD.

Working memory was also importantly impaired in our sample, as demonstrated by Digits Backward subtest of WAIS-R. Information storage by verbal working memory (measured in Digits Forward) and verbal content processing in working memory (measured in Digits Backward) are EFs highly sensitive to depressive mood states.

Verbal fluency was not importantly impaired in most cases of our sample, suggesting that the neural circuits involved in this cognitive function generally are not impacted by depressive state in bipolar elderly. In adults this finding might be different, since some authors have found important deficits in verbal fluency among depressive bipolar patients (Xu et al., 2012).

Executive dysfunction in elderly in the depressive phase of BD may be associated with lack of sufficient mental energy to run those cognitive processes that require larger amounts of effort to be performed. For instance, patients in our sample had more difficult in TMT-B than TMT-A, and in Stroop Test 3 than the other phases, suggesting that, as cognitive demand increases, their cognitive reserve is overpowered and, as a consequence, they cannot keep up with the growing executive demands. According to this hypothesis, this cognitive impairment would be reversible, returning to normal cognitive functioning as soon as patients switch their depressive state into an euthymic (normal mood) phase. Follow-up studies are required to test if this executive dysfunction in BD elderly is really transitory and completely dependent upon the affective phase of BD. One study has addressed cognitive outcomes in longitudinal assessment of old age euthymic BD (type I and II) and concluded that they did not exhibit accelerated cognitive decline over 2 years (Gildengers et al., 2012). Another study performs a systematic review about the neurocognitive dysfunction in BD and concluded that cognitive dysfunction is an enduring component and represents a core primary characteristic of BD, rather than being secondary to the mood state or medication, but they add that this core deficit can be confounded (either increased or attenuated) by the disease phase, in other words, depression may produce a temporary increase in the total amount of cognitive deficits seen in BD, which is in accordance with our view (Tsitsipa and Fountoulakis, 2015).

As a methodological limitation of our study, despite having restricted our sample only to the depressive phase of BD, this mood state in itself is very heterogeneous, varying from mild to severe depression. Future studies must try to control this variable.

In summary, executive dysfunction was very common in BD elderly patients in our sample, notwithstanding it was not severe in most of the cases. BD seems to contribute with additional burden to the aging process in the brain. Trail Making B, Stroop Test 3, Backward Digit Span and WCST represent a useful selection of tests sensitive to the specific executive dysfunction presented in old age bipolar depression. These tests seem more suitable than global screening cognitive measures frequently used in samples of elderly patients with cognitive impairment (e.g., the Mini-Mental State Examination; MMSE), which are likely not applicable in BD context due to low sensitivity (Burdick et al., 2015). The general pattern of specific executive deficits presented by our sample may suggest anomalous prefrontal-subcortical activation in elderly with BD. These cognitive findings can help understand some social and functional impairments seen in this disorder and indicate therapeutic targets as well as insights into its neurophysiopathology.

AUTHOR CONTRIBUTIONS

LC conception or design of the work; data collection; data analysis and interpretation; drafting the article. VS data collection; data analysis and interpretation. CS data collection; data analysis and interpretation. RV data collection; data analysis and interpretation; drafting the article. SF data collection; data analysis and interpretation. VC data collection; data analysis and interpretation. TA-F data collection; data analysis and interpretation; drafting the article.

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REFERENCES

Brooks, J. O. III, Bearden, C. E., Hoblyn, J. C., Woodard, S. A., and Ketter, T. A. (2010). Prefrontal and paralimbic metabolic dysregulation related to sustained attention in euthymic older adults with bipolar disorder. *Bipolar Disord.* 12, 866–874. doi: 10.1111/j.1399-5618.2010.00881.x

Burdick, K. E., Ketter, T. A., Goldberg, J. F., and Calabrese, J. R. (2015). Assessing cognitive function in bipolar disorder: challenges and recommendations for clinical trial design. *J. Clin. Psychiatry* 76, e342–e350. doi: 10.4088/JCP.14cs09399

Durston, S., Thomas, K. M., Yang, Y., Ulug, A. M., Zimmerman, R. D., and Casey, B. J. (2002). A neural basis for the development of inhibitory control. *Dev. Sci.* 5, F9–F16. doi: 10.1111/1467-7687.00235

Dybedal, G. S., Tanum, L., Sundet, K., Gaarden, T. L., and Bjølseth, T. M. (2013). Neuropsychological functioning in late-life depression. *Front. Psychol.* 4:381. doi: 10.3389/fpsyg.2013.00381

Faria, C. A., Alves, H. V. D., and Charchat-Fichman, H. (2015). The most frequently used tests for assessing executive functions in aging. *Dement. Neuropsychol.* 9, 149–155. doi: 10.1590/1980-57642015DN92000009

Gildengers, A. G., Chisholm, D., Butters, M. A., Anderson, S. J., Begley, A., Holm, M., et al. (2012). Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? *Psychol. Med.* 43, 801–811. doi: 10.1017/S0033291712001614

Heaton, K. R., Chelune, G. J., Talley, J. L., Kay, G. G., and Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual*. Odessa: Psychological Assessment Resources.

Kessler, U., Schoeyen, H. K., Andreassen, O. A., Eide, G. E., Hammar, Å., Malt, U. F., et al. (2013). Neurocognitive profiles in treatment-resistant bipolar I and bipolar II disorder depression. *BMC Psychiatry* 13:105. doi: 10.1186/1471-244X-13-105

Knopman, D. S., DeKosky, S. T., Cummings, J. L., Chui, H., Corey-Bloom, J., Relkin, N., et al. (2001). Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 56, 1143–1153.

Malloy-Diniz, L. F., Neves, F. S., Abrantes, S. S., Fuentes, D., and Corrêa, H. (2009). Suicide behavior and neuropsychological assessment of type I bipolar patients. *J. Affect. Disord.* 112, 231–236. doi: 10.1016/j.jad.2008.03.019

Ng, B., Camacho, A., Lara, D. R., Brunstein, M. G., Pinto, O. C., and Akiskal, H. S. (2008). A case series on the hypothesized connection between dementia and bipolar spectrum disorders: bipolar type VI? *J. Affect. Disord.* 107, 307–315. doi: 10.1016/j.jad.2007.08.018

Pantzar, A., Laukka, E. J., Atti, A. R., Fastbom, J., Fratiglioni, L., and Bäckman, L. (2014). Cognitive deficits in unipolar old-age depression: a population-based study. *Psychol. Med.* 44, 937–947. doi: 10.1017/S0033291713001736

Penfold, C., Vizueta, N., Townsend, J. D., Bookheimer, S. Y., and Altshuler, L. L. (2015). Frontal lobe hypoactivation in medication-free adults with bipolar II depression during response inhibition. *Psychiatry Res.* 23, 202–209. doi: 10.1016/j.pscychresns.2014.11.005

Rise, I. V., Haro, J. M., and Gjervan, B. (2016). Clinical features, comorbidity, and cognitive impairment in elderly bipolar patients. *Neuropsychiatr. Dis Treat.* 17, 1203–1213. doi: 10.2147/NDT.S100843

Sajatovic, M., Strejilevich, S. A., Gildengers, A. G., Dols, A., Al Jurdi, R. K., Forester, B. P., et al. (2015). A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord.* 17, 689–704. doi: 10.1111/bdi.12331

Samamé, C., Martino, D. J., and Strejilevich, S. A. (2013). A quantitative review of neurocognition in euthymic late-life bipolar disorder. *Bipolar Disord.* 15, 633–644. doi: 10.1111/bdi.12077

Schouws, S. N., Comijs, H. C., Stek, M. L., Dekker, J., Oostervink, F., Naarding, P., et al. (2009). Cognitive impairment in early and late bipolar disorder. *Am. J. Geriatr. Psychiatry* 17, 508–515. doi: 10.1097/JGP.0b013e31819e2d50

Schouws, S. N., Zoeteman, J. B., Comijs, H. C., Stek, M. L., and Beekman, A. T. (2007). Cognitive functioning in elderly patients with early-onset bipolar disorder. *Int. J. Geriatr. Psychiatry* 22, 856–861. doi: 10.1002/gps.1751

Tsitsipa, E., and Fountoulakis, K. N. (2015). The neurocognitive functioning in bipolar disorder: a systematic review of data. *Ann. Gen. Psychiatry* 14:42. doi: 10.1186/s12991-015-0081-z

Volkert, J., Haubner, J., Kazmaier, J., Glaser, F., Kopf, J., Kittel-Schneider, S., et al. (2016). Cognitive deficits in first-degree relatives of bipolar patients: the use of homogeneous subgroups in the search of cognitive endophenotypes. *J. Neural. Transm. (Vienna)* 123, 1001–1011. doi: 10.1007/s00702-016-1581-y

Xu, G., Lin, K., Rao, D., Dang, Y., Ouyang, H., Guo, Y., et al. (2012). Neuropsychological performance in bipolar I, bipolar II, and unipolar depression patients: a longitudinal, naturalistic study. *J. Affect. Disord.* 136, 328–339. doi: 10.1016/j.jad.2011.11.029

Young, R. C., Murphy, C. F., Heo, M., Schulberg, H. C., and Alexopoulos, G. S. (2006). Cognitive impairment in bipolar disorder in old age: literature review and findings in manic patients. *J. Affect. Disord.* 92, 125–131. doi: 10.1016/j.jad.2005.12.042

Zimmermann, N., Cardoso, C. O., Trentini, C. M., Grassi-Oliveira, R., and Fonseca, R. P. (2015). Brazilian preliminary norms and investigation of age and education effects on the Modified Wisconsin Card Sorting Test, Stroop Color and Word test and Digit Span test in adults. *Dement. Neuropsychol.* 9, 120–127. doi: 10.1590/1980-57642015DN92000006

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Brain Oscillatory Correlates of Altered Executive Functioning in Positive and Negative Symptomatic Schizophrenia Patients and Healthy Controls

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Working Memory and executive functioning deficits are core characteristics of patients suffering from schizophrenia. Electrophysiological research indicates that altered patterns of neural oscillatory mechanisms underpinning executive functioning are associated with the psychiatric disorder. Such brain oscillatory changes have been found in local amplitude differences at gamma and theta frequencies in task-specific cortical areas. Moreover, interregional interactions are also disrupted as signified by decreased phase coherence of fronto-posterior theta activity in schizophrenia patients. However, schizophrenia is not a one-dimensional psychiatric disorder but has various forms and expressions. A common distinction is between positive and negative symptomatology but most patients have both negative and positive symptoms to some extent. Here, we examined three groups—healthy controls, predominantly negative, and predominantly positive symptomatic schizophrenia patients—when performing a working memory task with increasing cognitive demand and increasing need for executive control. We analyzed brain oscillatory activity in the three groups separately and investigated how predominant symptomatology might explain differences in brain oscillatory patterns. Our results indicate that differences in task specific fronto-posterior network activity (i.e., executive control network) expressed by interregional phase synchronization are able to account for working memory dysfunctions between groups. Local changes in the theta and gamma frequency range also show differences between patients and healthy controls, and more importantly, between the two patient groups. We conclude that differences in oscillatory brain activation patterns related to executive processing can be an indicator for positive and negative symptomatology in schizophrenia. Furthermore, changes in cognitive and especially executive functioning in patients are expressed by alterations in a task-specific fronto-posterior connectivity even in the absence of behavioral impairment.

Keywords: positive and negative symptomatic schizophrenia, brain oscillations, executive functions, working memory, fronto-parietal network, theta, gamma

INTRODUCTION

Schizophrenia is a complex disorder comprised of widespread affective, cognitive, and behavioral disturbances and disruptions. The most widely used sub-classification of schizophrenia is the division into positive (hallucinations and delusions or confused thoughts and speech) and negative (anhedonia and withdrawal) symptomatology. Further core characteristics of the disorder are cognitive deficits such as disrupted memory processes, executive functioning, and attention. Such cognitive disturbances are usually equally present in patients showing predominantly negative or positive symptoms.

At the cortical level, patients suffering from schizophrenia (SZ) show large scale structural changes and alterations in the functional architecture of the brain. The condition is associated with significant gray and white matter volume losses (Kiriakopoulos et al., 2008; Huhlshoff Pol et al., 2002; Roalf et al., 2015; van Erp et al., 2015). Furthermore, fMRI studies indicate altered hemodynamic responses in distributed brain regions among SZ patients from sensory areas (Haenschel et al., 2009) to regions associated with higher-cognitive functioning (for a review see Ettinger et al., 2015). Electrophysiological studies also revealed dysfunctional electrophysiological activity in various parts of the cortex (Haenschel and Linden, 2011; Uhlhaas and Singer, 2015). The widespread structural and haemodynamic changes are a hallmark of schizophrenia. Yet the PFC seems to be disproportionately affected regarding structural but also functional changes (Wen et al., 2011; Zhou et al., 2015), and appears to contribute to patients' cognitive impairment (WM loss, attention deficit, impaired executive functioning, etc.).

Indeed several studies confirmed that dysactivation in the PFC is correlated with WM and executive functioning deficits (see Teffer and Semendeferi, 2012 for reviews; Etkin et al., 2013). In patients suffering from schizophrenia hypofrontality is most often reported where SZ patients display a pronounced decrease in prefrontal activation compared to healthy control participants while performance is usually but not necessarily affected (e.g., Carter et al., 1997; Callicott et al., 2003). Furthermore, Kerns et al. (2005) show that patients display reduced activity in the anterior cingulate cortex (ACC) during cognitive tasks, and that this reduction is associated with impaired conflict monitoring. In a meta-analysis by Glahn et al. (2005) clear support for hypofrontality in patients as compared to healthy controls was found. But the opposite seems to hold true in many cases; where patients consistently show increased activation (hyperfrontality) in prefrontal regions during working memory operations. Such hyperfrontality is normally interpreted as a compensatory mechanism (Callicott et al., 2003; Manoach, 2003). For example, Karlsgodt et al. (2007) found a strong positive association between the amount of prefrontal activation and performance. Manoach et al. (2000), on the other hand, report an increased prefrontal activation in SZ patients while performance was significantly impaired as compared to healthy controls. Taken together these studies indicate a less than uniform picture about frontal activation in patients with SZ during working memory task performance. What becomes clear, however, is that aberrant frontal activation during cognitive task performance and executive control is prominent in patients and might reflect general dysfunctions due to the disorder as well as mechanisms to compensate for those.

Thus, investigating WM, attention, executive control, and altered activity in the PFC seem to be a key factor for understanding the cognitive deficits associated with SZ. However, the above mentioned studies do not tell the entire story. Converging evidence suggests not only overall activation/deactivation as measured with brain imaging techniques but also transient and sustained EEG oscillatory mechanisms are crucial for understanding brain functioning in healthy as well as patient populations (Voytek and Knight, 2015). The exact timing of neuronal activity is important for information processing (e.g., O'Keefe and Recce, 1993; Singer and Gray, 1995) and rhythmic activity ranging from below 1 Hz to well above 100 Hz provide a time frame for neuronal synchrony (e.g., Buzsaki and Wang, 2012). Slow oscillations (e.g., theta 4–7 Hz) are associated with co-ordinating processes that span larger networks sometimes distributed across several cortical areas. Frontal theta oscillations—consistently found to originate in the ACC (e.g., Tsujimoto et al., 2006) are sensitive to task difficulty and prominent during maintenance and manipulation of information, during sustained attention and during unspecific processes of cognitive resource allocation (e.g., Gevins et al., 1997; Sauseng et al., 2007, 2010; Mitchell et al., 2008; Berger et al., 2014; Cavanagh and Frank, 2014). By contrast, gamma oscillations are mainly reported in connection to local information processing and co-ordination of activity in rather small networks. Gamma frequency oscillations are positively correlated with the BOLD signal and the firing of local neuronal assemblies (e.g., Roux and Uhlhaas, 2014).

A series of studies emphasizes that WM and attention deficits in patients with schizophrenia are accompanied by alterations in brain oscillatory activity. Gamma band-specific changes in the PFC are some of the most often reported oscillatory correlates of SZ, usually exhibiting lowered resting-state and task specific gamma activity (e.g., Cho et al., 2006; Basar-Eroglu et al., 2007; Gandal et al., 2012; Senkowski and Gallinat, 2015). However, contradicting findings also exist where SZ patients displayed stronger PFC gamma activity both during resting and cognitive operations in comparison to healthy control subjects (see e.g., Moran and Hong, 2011 or Senkowski and Gallinat, 2015 for a review). The dysregulation of GABAergic inhibitory neurotransmission—and hence imbalance between inhibition and excitation—is thought to underlie prefrontal gamma band changes. It might be one potential key mechanism responsible for many of the cognitive deficits in schizophrenia (Dasklakis et al., 2007; Uhlhaas and Singer, 2010; Lisman, 2012).

Another brain oscillatory pattern commonly found in SZ is increased low frequency brain activity in particular at theta, but also at delta frequencies (see Lisman, 2012 for a review). However, findings are also reported in the opposite direction where patients suffering from SZ display significantly less theta power than healthy control subjects (e.g., Koychev et al., 2012). This frontal—and especially medial frontal—slow frequency aberration in patients with SZ is well in line with their experienced deficits in WM and attention processes and

might either portray the impairment itself or alternatively, a compensatory mechanism to employ prefrontal resources to counter the deficit in cognitive processing. The controversial results regarding theta increase or decrease, however, are somewhat difficult to explain as the neurobiological mechanisms behind low frequency changes in SZ are less well identified than the ones behind fast frequencies. Furthermore, it is unclear whether low and high frequency changes are related or whether they are manifestations of two entirely separate neurobiological mechanisms (Uhlhaas and Singer, 2014).

Recent research identified local oscillatory and interregional coupling mechanisms driving allocation of attention and WM operations (Sauseng et al., 2005, 2010; Mizuhara and Yamagutchi, 2007; Wang et al., 2009; Ishii et al., 2014). Thereby, fronto-parietal neural synchronization seems to play a major role for executive functions. Given that executive control and WM operations are described as deficient in patients with SZ, it would make sense if the underlying neural correlates were affected by the disorder as well. And indeed, as Griesmayr et al. (2014) could show theta coherence between frontal and posterior cortical brain areas seems to be strongly decreased during a WM task in SZ patients as compared to healthy controls. In line with this, in a PET study, Meyer-Lindenberg et al. (2001) found aberrant fronto-posterior connectivity patterns as well as hypofrontality located in the ACC during a WM task in patients suffering from schizophrenia as compared to control subjects. Additionally, Popov et al. (2015) found decreased fronto-parietal connectivity (indexed by ACC theta phase to inferior parietal gamma amplitude coupling) in patients during increased demand for executive control. These findings are well in line with work demonstrating a general dysconnectivity in schizophrenia (see Uhlhaas and Singer, 2010; Schmitt et al., 2011). Rogasch et al. (2014), for instance, present evidence for dysconnectivity between task-dependently interacting cortical and subcortical areas in SZ as compared to healthy controls. Furthermore, they conclude that the inability to generate gamma oscillations in the PFC seems to be linked to higher positive symptomatology and cognitive impairment.

Findings highlighting specific symptoms being differentially linked to altered functional brain activity indicate that patients suffering from predominantly positive or predominantly negative symptoms might have differentially affected electrophysiological correlates of cognitive and especially executive functioning. This might also explain some of the above discussed controversial fMRI/EEG results. Lisman and Buzsaki (2008) for example argue that dysregulations of theta and gamma oscillations could result in very different symptoms; the former is responsible for confusion in the order of thoughts or percepts while the latter for memory deficits. Herrmann and Demiralp (2005) found that negative symptoms correlate with a decrease in gamma activity, whereas increased gamma activity was linked to positive symptoms such as hallucinations. Despite their high value for understanding the disorder itself, it might be a critical issue that most of the electrophysiological studies differentiating between positive and negative symptomatology look at the resting state activity in patients and healthy controls only. Importantly, however, in order to link findings regarding neural correlates of executive control and working memory deficits in SZ patients with their dysfunctional neuronal processes, it is vital to investigate patients during the execution of such a task. More specifically, we wanted to investigate and compare patients with predominantly positive and predominantly negative symptomatology regarding central executive difficulties in working memory. Additionally, the aim of this study was to investigate potential brain oscillatory signatures of central executive dysfunctioning at fast as well as slow EEG frequencies.

For this purpose we examined the difference between patients with predominantly negative symptoms, patients with predominantly positive symptoms and healthy control subjects that were tightly matched in gender, age and highest level of education during executing a visuo-spatial delayed-match-to-sample working memory task with high executive function demand while EEG was recorded. We investigated whether the two patient groups and healthy controls display differences in neuronal processing in the theta and gamma frequency bands in the ACC as well as the posterior parietal cortex (right and left BA40). As outlined above these frequency bands seem to be critically involved in complex working memory operations and the specified regions of interest are crucial for fronto-parietal executive control processes. Finally, we wanted to know whether patients and control subjects differ in terms of fronto-parietal communication during a working memory task with high central executive load. Our study aims at understanding alterations of working memory related brain oscillatory activity in patients suffering from schizophrenia predominated by different symptomatologies (negative and positive). Thereby we are trying to fill a gap in the understanding of this complex disorder as, to our knowledge, there is no research that has investigated these schizophrenia sub-populations in such a manner.

MATERIALS AND METHODS

The here reported data are a reanalysis of part of the data previously published by Griesmayr et al. (2014). In comparison to this earlier publication, however, the analyzed sample was divided according to symptomatology; i.e., patients suffering from predominantly positive symptomatic and predominantly negative symptomatic schizophrenia. Moreover, in the current paper data were analyzed in EEG source space in order to identify the effects in specific regions crucially implicated in the fronto-parietal control network.

Participants

Twenty-seven patients meeting ICD 10- criteria for schizophrenia participated in the study. Patients were recruited from the in- and outpatient facilities of the "Christian-Doppler Klinik Salzburg." They had normal or corrected to normal vision and intact color vision. None of the patients showed a history of neurological illness or had alcohol or substance abuse within the last month prior to study participation. Further criteria for participation were that pharmacological treatment was stable and that they did not have acute florid

symptomatology. Seven participants had to be excluded from data analysis because they could not finish the task ($n = 3$), the EEG was too heavily contaminated with artifacts ($n = 4$). Severity of clinical symptomatology was assessed with the PANSS (Positive and Negative Syndrome Scale; Kay et al., 1987) by trained psychiatrists. The obtained scores were used to classify patients either as "predominantly negative symptomatic" or "predominantly positive symptomatic" (later referred to as NEG and POS, respectively) which resulted in the two patient sub-groups (NEG and POS) with 10 patients each (see **Table 1** for details and statistical comparisons). The two patient groups were matched according to age, gender, and highest education level. The diagnostic subgroups of the NEG and POS groups were paranoid schizophrenia (NEG: $n = 7$; POS: $n = 9$), undifferentiated schizophrenia (NEG: $n = 1$) and schizoaffective disorder (NEG: $n = 1$; POS: $n = 2$). Patients received treatment with atypical (NEG: $n = 9$; POS: $n = 5$), typical (POS: $n = 2$), and combined atypical and typical (NEG: $n = 1$; POS: $n = 3$) antipsychotics. Additionally, some participants received low doses of benzodiazepines (POS: $n = 3$) and/or antidepressants (NEG: $n = 5$; POS: $n = 3$). The mean chlorpromazine equivalent for NEG was 321.67 mg/day (SD = 257.92) and for POS 806.68 mg/day (SD = 326.87) (see Möller et al., 2000; Woods, 2003; see **Table 1** for statistical comparisons).

The 10 healthy control participants (later referred to as CON group) are a sub-set of the 21 healthy controls used by Griesmayr et al. (2014). They were matched to the two patient groups according to age, gender and level of highest education. Prior to testing they completed the Brief Symptom Inventory (Franke, 2000) which screens for clinically relevant psychological stress symptoms and the Structured Clinical Interview (SCI-I) to check for any mental disorders. Moreover, participants were excluded if they had any neurological diseases or first-degree relatives with a psychiatric disorder as well as when they reported alcohol or substance abuse within the last month prior to study participation.

All participants gave a written informed consent and were monetarily reimbursed for participation. The study was approved by the ethics committee of the Federal State of Salzburg and conducted in agreement with the Declaration of Helsinki.

Experimental Procedure

Participants performed a visuo-spatial delayed-match-to-sample working memory task in a dimly lit room. The stimuli were presented centrally on a computer screen with Presentation® 0.71. The memory set was presented at the beginning of each trial for 700 ms as a 6 × 6 matrix (visual angle of 9.2° × 9.2°) in which either one (load 1) or three (load 3) colored squares were presented. Additionally, if the squares were green, participants simply needed to retain their position for a delay period of 2000 ms (retention task); while if the squares were red they needed to mentally rotate their positions around a vertical line in the middle of the matrix (manipulation task) during the delay interval. During the 2000 ms delay period a mask was presented to prevent afterimages. Thereafter, a probe matrix was presented in which one or three (depending on load) gray squares were presented for a further 2000 ms. Participants then needed to indicate by mouse button press whether the square locations in the probe matrix matched the memory set or not (or the mentally rotated version thereof, depending on task). For non-match trials one of the squares in the probe matrix was shifted for one location. Between trials participants saw a fixation cross (duration jittered between 2100 and 2500 ms; see **Figure 1** for depiction of trial structure and stimulus example). Participants were instructed to answer as correctly as possible.

In total 224 trials were presented which resulted in 56 trials per condition—retention load 1 (RETL1), retention load 3 (RETL3), manipulation load 1 (MANL1), and manipulation load 3 (MANL3)—of which half were match and half were non-match. Trials were presented in randomized order and a practice block was carried out before the start of the actual experiment.

EEG Recording

Data were recorded from 28 Ag-AgCl ring electrodes (Easycap®) mounted according to the international 10–20 system: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP5, CPz, CP6, T5, P3, Pz, P4, T6, PO3, PO4, O1, Oz, O2; against two reference electrodes placed on the earlobes. The ground electrode was placed on the forehead and eye movements were recorded with an electrode each above and next to the right eye. The EEG signal was registered between 0.016 and 80 Hz with a sampling rate of 1000 Hz and a notch-filter set at 50 Hz using a BrainAmp MR+ amplifier (Brain Products®). Impedances were kept below 15 kΩ.

Data Analysis

Behavioral Data Analysis

For behavioral data analysis IBM SPSS Statistics 22 was used. The accuracy (percentage of correctly performed trials) was analyzed using Wilcoxon Signed Rank test to examine the difference in performance comparing low-load and high-load conditions, as well as, the retention and the manipulation task, irrespective of the group of participants. The impact of the participants' group on the accuracy was further tested with a series of Kruskal-Wallis tests.

EEG Data Analysis Pre-processing

For EEG data analysis Brain Vision Analyzer 2.0 (Brain Products®) and in-house Matlab R2014b scripts (Math Works®) were used and statistical analyses were performed with IBM SPSS Statistics 22 and Matlab. Data were first offline re-referenced to digitally linked earlobes and high-pass filtered with a low cut-off at 1 Hz (48 db/Oct Butterworth Zero Phase IIR Filter as implemented in BrainVision Analyzer 2.0). In order to remove horizontal and vertical eye movements and blinks, independent component analysis (ICA) ocular correction was applied to the filtered raw EEG data. Remaining artifacts were removed by visual inspection. Then data were segmented (from 1000 ms pre-stimulus onset to 3000 after stimulus onset, in respect to the memory set) for every condition separately as the focus of the analysis was on the delay interval; i.e., when participant retained the location of the square(s) or mentally rotated them. On average this resulted in 45.97 (SD = 4.82) artifact free trials for RETL1, 46.7 (SD = 5.02) for RETL3, 44.4 (SD = 4.77) for

TABLE 1 | Demographic and clinical characteristics (*p*-values represent the significance of the performed Kruskal–Wallis tests between groups, except gender, and education, which were tested with chi-square tests).

	Controls	Negative symptomatic sub-group	Positive symptomatic sub-group	*p*-values
N	10	10	10	
Age	33.50 ± 2.87	31.60 ± 2.59	32.80 ± 2.43	$p = 0.925$
Gender (male/female)	6/10	7/10	8/10	$p = 0.621$
PANSS overall	–	78.66 ± 23.91	77.11 ± 20.91	$p = 0.880$
PANSS neg.sympt.	–	24.67 ± 3.03	14.56 ± 1.51	$p = 0.015$
PANSS pos.sympt.	–	16.67 ± 2.12	21.67 ± 2.78	$p = 0.138$
Education				$p = 0.312$
Higher degree	3	3	0	
A-levels	5	4	3	
Apprenticeship/professional school	1	1	3	
Elementary school	1	2	4	
Colrpromazine (mg/day)	–	321.67 ± 257.92	806.68 ± 326.87	$p = 0.002$

MANL1 and 47.57 (SD = 4.13) for MANL3. An estimation of the electrophysiological activity at source space was then calculated using the LORETA algorithm implemented in Brain Vision Analyzer 2.0 (see Pascual-Marqui et al., 1994). The algorithm transforms the scalp-level EEG data into a time series of current source density in pre-defined regions of interest (ROIs) in 3D-source space for each single trial. The ROIs were specified in line with the fronto-parietal network hypothesis outlined in the introduction; this resulted in one ROI in the bilateral ACC and one in the right BA40 (posterior parietal cortex bordering the IPS) and one in the left BA40.

Instantaneous Amplitude

To obtain the instantaneous amplitude of theta and gamma frequencies in these regions, two individual continuous complex Morlet wavelet transformations were calculated for slow and fast frequencies, respectively. For slow frequencies a 5-cycle Morlet wavelet was used to analyse the frequency range from 3 to 15 Hz in 13 frequency steps. For fast frequencies a 10-cycle Morlet wavelet transform was calculated from 30 to 80 Hz in 6 frequency steps. Any further analysis was done using in-house Matlab R2014b scripts (Math Works®). In order to account for outliers we used a conventional cut-off of ±3.29 standard deviations for every subject and every data point across trials. Values that exceeded this individual cut-off were set to the value representing ±3.29 times the standard deviation. This was done to attenuate the impact of extreme values without having to remove the whole trial. For the calculation of changes in the instantaneous amplitude of theta and gamma oscillations during the 2000 ms retention/manipulation interval the instantaneous amplitude values were first averaged across trials. The power values of both, theta and gamma frequencies were decibel transformed (see (Cohen and Ridderinkhof, 2013) for more details) according to a baseline period from 500 to 200 ms prior to stimulus onset. Decibel conversion was used in order to ensure comparability between all frequencies, conditions, groups or subjects and time points as it brings all data to the same scale. Frequency bins between 4 and 8 Hz were averaged to obtain a theta band, and frequency bins between 30 and 50 Hz and between 50 and 80 Hz were averaged into a slow and a fast gamma band, respectively. Finally, the decibel transformed amplitude values for the three frequency bands were averaged into four time windows of 500 ms each between stimulus-offset and probe-onset. For statistical comparisons the average decibel transformed amplitude values for each time window were exported for each condition (RETL1, RETL3, MANL1, and MANL3) and each individual subject and analyzed in IBM SPSS Statistics 22 with a mixed-model ANOVA with the three within-subject factors: task (RET, MAN), load (L1, L3), and time window (1–4; Time); and the between-subject factor: group (NEG, POS, CON). This statistical procedure was repeated for each frequency band and each ROI separately. *Post-hoc* tests were Bonferroni corrected and when assumption of sphericity was not met data were Huynh-Feldt corrected.

Phase Synchronization

In order to obtain theta phase values for calculations of the phase locking value (PLV) the phase of theta (center frequency of 6; 5 cycles complex continuous Morlet wavelet) was estimated between −pi and +pi in Brain Vision Analyzer 2.0 and then exported into Matlab to be further analyzed using in-house scripts. To assess whether theta phase estimated from the ACC is locked to the theta phases as obtained from the right and left BA40 the PLV was calculated according to Lachaux et al. (1999). The PLV is a measure of interregional phase synchronization by assessing the inter-trial variability of phase differences between signals from two distinct sources at any given time point. The PLV can range from zero to one, where a value of 1 indicates perfect stability of phase differences between the two signals across trials, and a value of 0 indicates completely random distribution of phase differences. First, the theta phase differences were calculated between two ROIs (frontal and right or left parietal) for every time point in every trial (2000 ms of delay period) for every condition and every participant separately. Then the values across trials were averaged and finally the data within the 2000 ms delay period were again averaged into four time windows of 500 ms each (see instantaneous amplitude). For

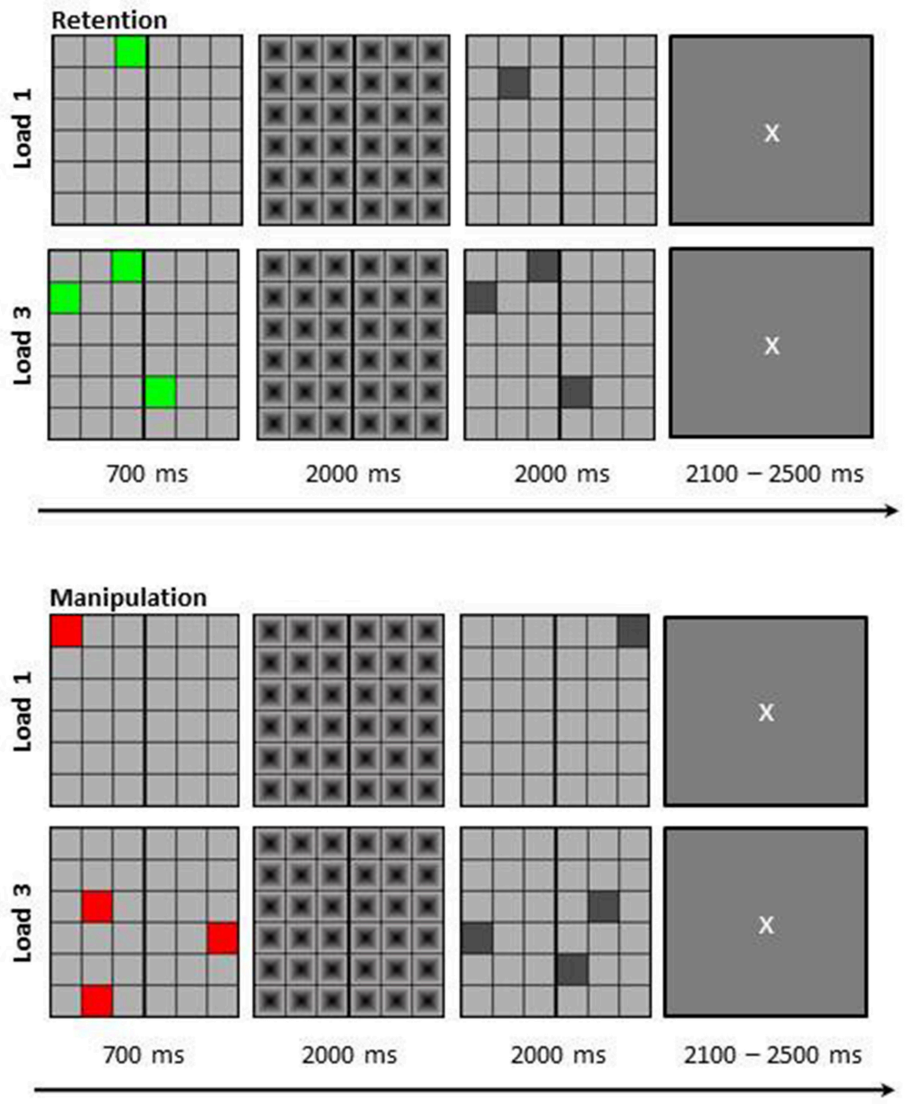

FIGURE 1 | Schematic depiction of the visuo-spatial delayed match to sample working memory task. Participants had to either retain the positions of the colored squares (Retention) or mirror their positions around the vertical line (Manipulation). The load was either one item (L1) or three items (L3). Figure taken with permission from Griesmayr et al. (2014).

statistical analysis the PLV values were analyzed in IBM SPSS Statistics 22 with a mixed-model ANOVA with the three within-subject factors: condition (RET, MAN), load (L1, L3), and time window (1–4); and the between-subject factor: group (NEG, POS, CON) for the right and the left BA40 separately.

RESULTS

Behavioral Results

The analysis of the behavioral data showed that the accuracy was significantly lower in the high-load (L3) than in the low-load (L1) condition in the retention task ($Mdn_{L1} = 98.21$, $Mdn_{L3} = 97.32$), $Z = -2.38$, $p = 0.017$, and in the manipulation task ($Mdn_{L1} = 96.43$, $Mdn_{L3} = 83.04$), $Z = -4.79$, $p < 0.001$. Further analysis showed that the accuracy was affected not only by the load, but also by the task. That is the accuracy was significantly lower in the manipulation task at low-load, $Z = -2.71$, $p = 0.007$ and at high load $Z = -4.79$, $p < 0.001$ in comparison to the retention task.

Importantly, the performed analysis on the accuracy between the three groups (negative symptomatic, positive symptomatic patients, and healthy controls) revealed no significant effect in either of the tasks at neither load. More specifically, the accuracy of the NEG, POS, and CON groups showed no significant difference in the retention task at low-load (L1), $H_{(2)} = 3.28$, $p = 0.19$, and at high-load (L3), $H_{(2)} = 3.28$, $p = 0.19$, or in the manipulation task at low-load (L1), $H_{(2)} = 0.34$, $p = 0.846$, and at high-load, $H_{(2)} = 1.02$, $p = 0.602$.

In sum the behavioral result suggest that accuracy was influenced by load and also by task. Participants performed better in the low-load conditions and in the retention task. Importantly, the three groups showed similar behavior performance, i.e., the control group performed no better than the patient groups (see **Table 2** for accuracy values).

Instantaneous Amplitude

ACC Theta

Analysis of the task-specific instantaneous theta amplitude values in the ACC revealed a main effect of Task, $F_{(1,\ 27)} = 10.85$, $p = 0.003$, indicating that the manipulation task was associated with higher theta amplitude in the ACC than the retention task. Furthermore, the main effect of Load was also significant, $F_{(1,\ 27)} = 9.59$, $p = 0.005$, because of the higher theta amplitude in the high-load (L3) condition. In addition, the also significant main effect of Time (1–4), $F_{(1.88,\ 50.7)} = 10.94$, $p < 0.001$, was the result of the attenuation of the theta amplitude increase (as to baseline) over the course of the delay period.

In addition, interaction effects [Load × Time, $F_{(2.6,\ 70.18)} = 10.69$, $p < 0.001$; Task × Time interaction, $F_{(2.57,\ 68.74)} = 8.2$, $p < 0.001$] indicate that theta stays higher over the course of the whole delay period for the more difficult conditions (i.e., higher load and manipulation task). Finally, a Task × Load × Time × Group four-way interaction effect also reached significance, $F_{(5.95,\ 80.31)} = 2.55$, $p = 0.026$. Further testing showed that in the control group the theta power increase (as to baseline) showed consistent attenuation over the course of the delay period for the retention task in general and for the low-load condition of the manipulation task [main effect of Time $F_{\mathrm{RetL1}(3,\ 27)} = 8.87$, $p < 0.001$; $F_{\mathrm{RetL3}(3,\ 27)} = 17.94$, $p < 0.001$; $F_{\mathrm{ManL1}(3,\ 27)} = 13.41$, $p < 0.001$]; whereas it did not drop over time in the high-load manipulation condition [Time $F_{\mathrm{ManL3}(3,\ 27)} = 0.9$; $p = 0.455$]. The negative symptomatic group showed a pattern similar to the controls in the low-load retention condition [Time $F_{\mathrm{RetL1}(1.3,\ 11.8)} = 5.84$, $p = 0.026$] but with a less pronounced attenuation of theta power. However, theta power was sustained not only in the manipulation high-load but also in the low-load and retention high-load condition [Time $F_{\mathrm{RetL3}(1.8,\ 16.3)} = 0.31$, $p = 0.715$; $F_{\mathrm{ManL3}(1.4,\ 12.9)} = 0.1$, $p = 0.845$; $F_{\mathrm{ManL1}(3,\ 27)} = 2.48$, $p = 0.083$]. The positive symptomatic group displayed rather sustained theta power over the course of the delay period in all conditions except low-load retention condition [Time $F_{\mathrm{RetL1}(3,\ 27)} = 8.62$, $p < 0.001$; $F_{\mathrm{RetL3}(3,\ 27)} = 2.22$, $p = 0.109$; $F_{\mathrm{ManL1}(3,\ 27)} = 2.99$, $p = 0.052$; $F_{\mathrm{ManL3}(1.8,\ 16.6)} = 1.29$, $p = 0.300$]; with the high-load manipulation condition showing even a slight steady increase over the delay period (see **Figure 2**).

Overall, these results suggest that ACC theta amplitude was increased in the high-load condition and in the manipulation task and that theta amplitude was particularly pronounced during the early time windows of the delay period. Furthermore, the decrease over the course of the delay period was smaller in the high-load condition and in the manipulation task.

ACC Gamma

The only effect that was significant in the analysis of the low-gamma band, was a main effect of Time, $F_{(2.56,\ 66.47)} = 5.79$,

TABLE 2 | Mean accuracy with standard error across groups, conditions, and load.

	Retention		Manipulation	
	Load 1	*Load 3*	*Load 1*	*Load 3*
CON	95.18 ± 3.25	93.04 ± 3.41	93.57 ± 2.58	81.79 ± 3.73
NEG	98.39 ± 0.62	97.50 ± 1.07	96.07 ± 0.95	83.22 ± 1.49
POS	97.14 ± 0.48	93.22 ± 2.01	94.64 ± 1.38	79.82 ± 2.61
Total	96.90 ± 1.10	94.58 ± 1.37	94.76 ± 1.01	81.61 ± 1.56

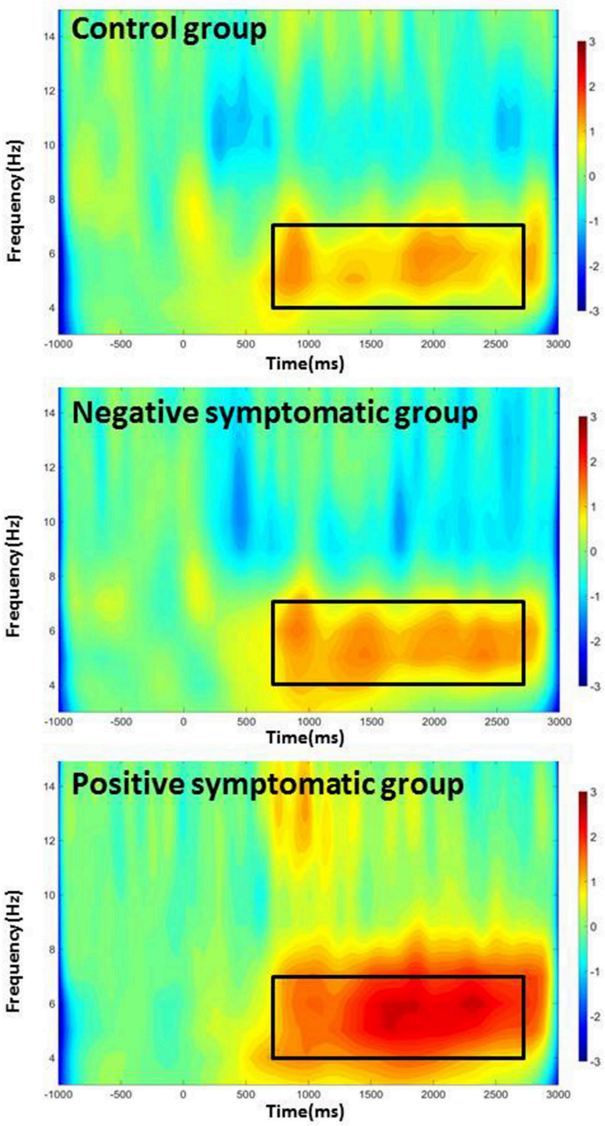

FIGURE 2 | Frontal theta band activity for the high-load manipulation condition for all three groups. The frequency of interest (4–7 Hz) and time period of interest (delay period) are indicated with a frame.

$p = 0.002$, indicating higher gamma power during the second part of the delay period, irrespective of task, load and group.

The analysis in the high gamma range revealed a main effect of Time, $F_{(1.92,\ 51.85)} = 5.82$, $p = 0.006$, which was driven by the increase of gamma power over the course of the delay period. Furthermore, central to our hypothesis, a marginally significant Load × Group interaction effect was found, $F_{(2,\ 27)} = 3.1$, $p = 0.061$ (see **Figure 3**). *Post-hoc* ANOVAs performed separately on low-load and high-load trials showed that whilst in the low-load condition, no significant main effect or interaction involving Group emerged, in the high-load condition a main effect of Group reached significance, $F_{(1,\ 27)} = 3.48$, $p = 0.045$. Importantly, the Bonferroni corrected ($p_{crit} < 0.017$) pairwise comparisons showed a significant difference only between positive and negative symptomatic groups, $t_{(18)} = 2.65$, $p = 0.016$, indicating higher gamma power in the negative symptomatic group than in the positive symptomatic group at high-load. In fact, further *post-hoc* repeated-measures ANOVA carried out on the positive and negative symptomatic group data separately suggested that, whereas in the negative symptomatic group the gamma power significantly increased from low-load to high-load conditions, $F_{(1,\ 9)} = 6.29$, $p = 0.034$, there was no difference in the positive symptomatic group gamma power across the same conditions (see **Figure 3**).

To summarize the above results, in the lower gamma frequency range the only significant finding suggested amplitude increase over the delay period. Similarly, high gamma amplitude also increased over the delay period; but importantly, amplitude was differentially affected by the factor group in the high- and low-load conditions. Whereas, in the low-load condition there was no difference among the groups, in the high-load condition gamma power was significantly higher in the negative symptomatic group than in the positive symptomatic group.

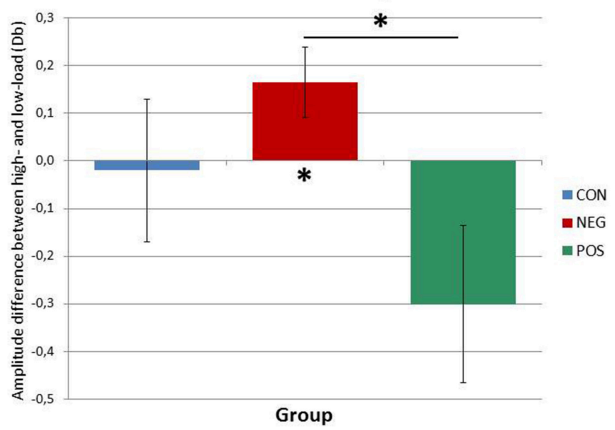

FIGURE 3 | Frontal gamma amplitude differences between high-load and low-load conditions for the three groups. While the positive symptomatic group shows decreased gamma power in the ACC in the high-load condition, the negative symptomatic group displays a marked increase. The healthy control subjects do not differ from either patient group. Significant differences are indicated by asterisks ($p < 0.05$).

BA40 Theta

Theta power in the right parietal ROI was modulated by several factors as a series of main and interaction effects showed. The strongly significant main effect of Time, $F_{(2.39,\ 64.62)} = 11.57$, $p < 0.001$, reflected the fact that theta amplitude was higher in the earlier time windows and showed a decrease over the course of the delay period.

Importantly, the results also indicated significant Time × Group, $F_{(4.79,\ 64.62)} = 2.60$, $p = 0.035$, and Task × Group interaction effects, $F_{(2,\ 27)} = 3.55$, $p = 0.043$. The former suggests that the decrease of theta power over the delay period was further modulated by the Group factor. Additional separate ANOVAs for each group individually revealed that there is no significant effect of Time in the healthy controls and the positive symptomatic group but a strongly significant main effect of Time in the negative symptomatic group $F_{(3,\ 9)} = 13.73$, $p < 0.001$; showing a decrease of theta power over the course of the delay period in the right BA40.

Furthermore, the above-mentioned significant Task × Group interaction effect was primarily driven by the fact that while the control group had increased theta power in the manipulation task compared to the retention task (irrespective of load), $F_{(1,\ 9)} = 7.21$, $p = 0.025$, the positive symptomatic group displayed a marginally significant decrease in the manipulation as compared to the retention task $F_{(1,\ 9)} = 3.88$, $p = 0.08$, and the negative symptomatic group displayed no significant difference.

Finally, the analysis of the left parietal ROI also showed a significant main effect of Time, $F_{(2.22,\ 59.87)} = 31.65$, $p < 0.001$ and a marginally significant main effect of Load, $F_{(1,\ 27)} = 4.16$, $p = 0.051$. The main effect of time indicated that over the course of the delay period theta power decreased.

To sum up, theta power in the right parietal ROI decreased over the delay period. This decrease was only significant in the negative symptomatic group but not in the other two groups. In addition, theta power was higher in the manipulation task compared to the retention task in the control group but not different between the two tasks in the patient groups.

BA40 Gamma

No significant effects were found in the lower gamma band in the right BA40 and in the lower and high gamma band in the left BA40.

In the high gamma band the interaction effect Task × Load × Time was marginally significant $F_{(2.99,\ 80.76)} = 2.7$, $p = 0.052$ and the four-way interaction Task × Load × Time × Group reached a significant level $F_{(5.98,\ 80.76)} = 3.99$, $p = 0.002$ in the right BA40. Further investigation of the Task × Load × Time effect showed that while there was no task-dependent difference in right BA40 gamma power in the retention task (low- and high-load) and the high-load condition of the manipulation task; there was a marginally significant increase in the low-load condition of the manipulation task $F_{(2.2,\ 63.7)} = 2.94$, $p = 0.055$.

In order to explain the four-way interaction separate ANOVAs for the four conditions (RETL1, RETL3, MANL1, and MANL3) were run. No significant effects were found for the low-load and high-load retention and low-load manipulation conditions. In the high-load manipulation condition the controls displayed

an increase in gamma amplitude over time, while the negative symptomatic group showed a decrease. The positive symptomatic group showed a pattern where there is a decrease in the early delay period and then an increase in the later time windows.

Phase Synchronization

The PLV of the theta frequency band between the ACC and right BA40 showed a highly significant Group effect, $F_{(1, 27)} = 14.85$, $p < 0.001$. Further *post-hoc* tests revealed that the control group had significantly higher PLV than the negative ($p = 0.001$), and also the positive symptomatic groups ($p < 0.001$), whereas the PLV did not differ significantly between the two patient groups ($p = 0.654$).

In addition to this main effect, a significant Load × Time × Group, $F_{(6, 81)} = 2.28$, $p = 0.044$ three-way interaction effect was found (see **Figure 4**). Investigation of this three-way interaction indicated that the controls and positive symptomatic group displayed the same amount of theta phase synchronization over time for the low-load and high-load conditions while the negative symptomatic group showed a significant Load × Time interaction $F_{(3, 27)} = 5.88$, $p = 0.003$ indicating that there is a rather transient increase in phase synchronization in the low-load condition in the first half of the delay period. The high-load condition, on the other hand, shows a more sustained increase of phase synchronization over the course of the delay period.

Overall, these results indicate significantly stronger fronto-posterior theta phase synchronization in the healthy controls as compared to the patient groups.

DISCUSSION

Executive functions have previously been shown to employ a network of cortical structures spanning prefrontal areas, in particular the ACC, and right posterior parietal regions. This network is strongly involved in working memory and operations requiring cognitive control. Both, executive functions as well as the underlying neuronal network have been found to be compromised in schizophrenia. However, little is known about what it is exactly that underlies those dysfunctions. Furthermore, even less is known about the brain oscillatory correlates of the complex and highly diverse symptomatology of schizophrenia (i.e., negative and positive symptomatology) and its relation to executive functioning.

In this article we examined schizophrenia patients with predominantly negative symptomatology, with predominantly positive symptomatology and healthy control subjects. We recorded EEG while they performed a visuo-spatial delayed match to sample working memory task with varying load and varying need to employ executive functions. We investigated the delay period of the WM task and compared the three groups in respect to performance and brain oscillatory activity. We investigated areas of the fronto-parietal executive control network (ACC and right BA40 as well as left BA40) by looking at local amplitude changes of theta and gamma oscillations; two frequencies repeatedly found to be strongly implicated in visual working memory operations in these areas. Moreover, we investigated communication within this network by analysing phase synchrony in the theta frequency between the frontal and the parietal regions of interest. We hypothesized that patients would show a different pattern of functional cortical activation as compared to healthy controls. Furthermore, we expected the two patient groups to display differences in brain oscillatory correlates of executive functioning, given that their different symptomatologies greatly differ in their behavioral expression.

A very robust finding in this study is that sustained phase synchronization in the theta frequency between the ACC and the right (but not the left) BA40 was significantly disrupted in the patient groups as compared to controls (see **Figure 4**). Similar results were also obtained on scalp level by Griesmayr et al. (2014) where the 21 patients—as one sample—were compared with 21 matched healthy control subjects. Moreover, these findings are very well in line with the dysconnectivity theory of schizophrenia (e.g., Uhlhaas and Singer, 2010; Rogasch et al., 2014) stating that global cortical communication is disrupted in patients suffering from SZ. During working memory operations that require executive functions it is repeatedly found that theta oscillations in prefrontal areas are synchronized with theta oscillations in posterior parietal regions. This long-range communication is said to underlie (top–down) executive control from frontal areas interacting with local posterior information processing (e.g., Sauseng et al., 2005; Wu et al., 2007; Sauseng et al., 2008). Given that executive functions are often impaired in SZ, it stands to reason that such long-range theta coherence should also be disrupted. In our case, however, this pattern of dysconnectivity in SZ patients was not related to impaired task execution, i.e., patients did do just as well as the healthy control subjects.

In addition to theta long-range synchronization, the patients were also distinguishable from the healthy control subjects by the amount of local theta power difference between the retention and the manipulation tasks in the right BA40. While the healthy controls showed a markedly higher theta activity in the right posterior ROI in the manipulation task as compared to the retention task, the patient groups displayed no such load-dependent increase during the delay period. Posterior theta activity has been found to increase during working memory operations (e.g., Osipova et al., 2006; see Roux and Uhlhaas, 2014 for a review) and increasing load and has been linked to determining WM capacity (e.g., Moran et al., 2010). Hence, an increase in posterior theta activity from the retention to the manipulation task is not surprising. Such a task/load-dependent increase was also found in the ACC for all three groups; where theta power was significantly higher for the high-load and manipulation task as compared to low-load and retention task. What is curious, however, is that while patients displayed such task-dependent increase in theta power in the ACC, they did not show this pattern of increasing theta power in the BA40. Moreover, the positive symptomatic group was distinct from the healthy controls and the negative symptomatic group by the pattern of ACC theta activity mainly in the manipulation high-load condition (see **Figure 2**). The positive symptomatic patient group seemed to employ generally more sustained frontal theta activity in all conditions over time and even displayed an increase over the course of the delay period in the most difficult (high-load manipulation) condition. Given that frontal theta increase is

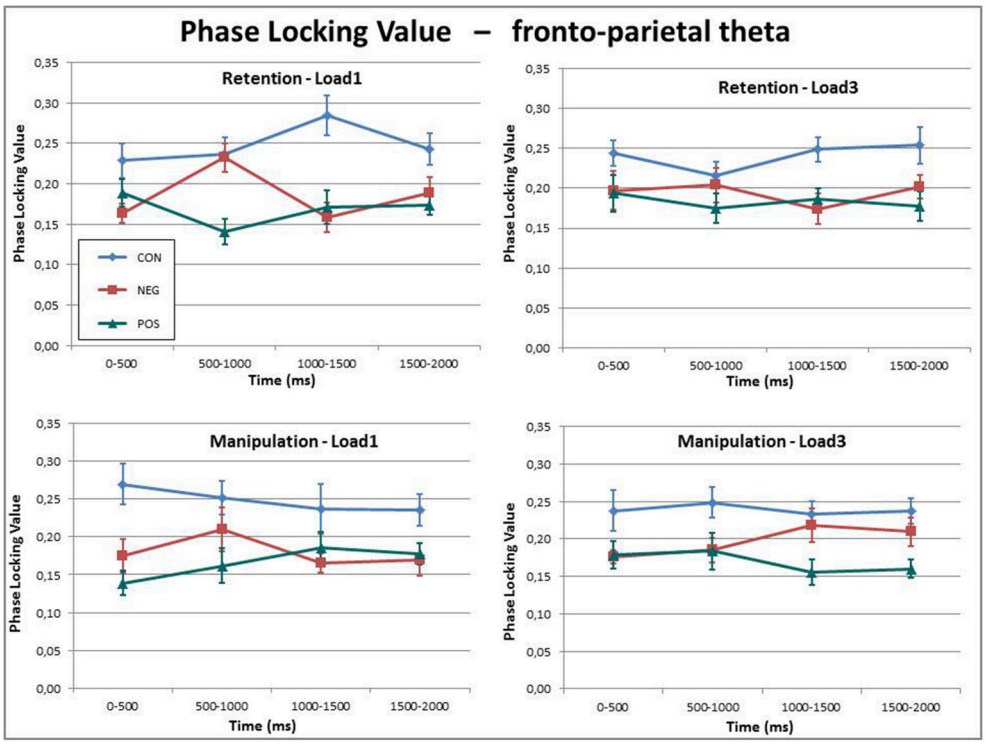

FIGURE 4 | Theta phase synchronization between the ACC and the BA40 indexed by phase locking values (PLVs) for all three groups in the four conditions over the delay period. While the phase synchronization is fairly constant over time and between conditions, the healthy control subjects display a generally higher phase synchronization than the two patient groups.

a strong indicator for executive control (e.g., Gevins et al., 1997) this might hint at the employment of some sort of compensatory mechanism which recruits more executive processing power to successfully complete the task at hand.

Interestingly, we also found an effect in the high gamma frequency range in the ACC differentiating the two patient groups (see **Figure 3**). While gamma power did not differ between the three groups in the low-load conditions, the negative symptomatic patient group displayed significantly stronger gamma power than the positive symptomatic group in the high-load conditions. In fact, while local gamma power in the ACC increased from the low- to the high-load condition in the negative symptomatic group, the positive symptomatic group showed no difference between the two conditions. This finding suggests that local frontal information processing represented by gamma oscillatory activity seems to be aberrant in SZ and might be a key factor in differentiating the neural underpinnings of the different symptomatologies of the disorder. It is a finding well in line with the suggestion by Rogasch et al. (2014) that decreased prefrontal gamma activity is strongly linked to positive symptomatology. Furthermore, such differences between the patient groups might play a major role in explaining contradictory findings in literature where some authors find decreased frontal gamma in SZ while others find the opposite pattern (see Senkowski and Gallinat, 2015 for a review).

Another, although less robust effect indicated that theta power was attenuated over the time course of the delay period in the right parietal area in the negative symptomatic group whereas it stayed constant in the positive symptomatic group and in healthy control participants indicating consistent engagement with the to-be-retained information. As the area is thought to be strongly involved in visuospatial processing (Moscovitch et al., 1995) and there is evidence suggesting that the theta frequency band is particularly relevant in such processing (Romei et al., 2011), the disproportionate reduction of theta power could have a negative impact on visuospatial working memory. However, this different pattern in the negative symptomatic group does not necessarily reflect impairment: Firstly, their behavioral performance was not impaired as compared to the other two groups; and secondly, they seem to show a generally slightly different oscillatory pattern in this task than controls and positive symptomatic patients. This might partly reflect parallel mechanisms to compensate for the comprised parietal theta activity (see for instance the ACC gamma activity differences between negative symptomatic and the other two groups). To draw any clear conclusions further studies would be needed to investigate the exact nature and relevance of this effect more in depth.

In the current study we only found local and fronto-parietal coupling results in the right but not the left parietal ROI. This might be because of the material type (i.e., strictly spatial information processing) or the required attention network.

The right parietal region is strongly linked to visuospatial processing and moreover to sustained attention to spatial locations (e.g., Smith et al., 1996; Malhotra et al., 2009; Jackson et al., 2011). A right hemispheric dominance for visuospatial processing, representation and working memory has been shown in both, primates and humans with neuropsychological and neuroimaging techniques as well as in neurostimulation studies (e.g., Pisella et al., 2011; for reviews see Oleksiak et al., 2011; Pisella, 2016). However, we want to point out that the role of the right parietal cortex in visuospatial cognition is not yet fully understood and that visual working memory processing and attention is not exclusively right lateralised (e.g., Cowan et al., 2011 for color processing; Majerus et al., 2010 for faces; Popov et al., 2015 for executive functioning).

Generally, our results suggest that patients suffering from schizophrenia display altered oscillatory patterns during executive processes indicated by disrupted fronto-parietal theta synchronization in the executive network and local right parietal theta activity, indicating differential local neural processes. Importantly, local ACC gamma and to a lesser extent right parietal and ACC theta also have differential patterns between positive and negative symptomatic SZ patients, but long-range fronto-parietal coupling did not distinguish the two patient groups but only patients and healthy controls. It is important to point out that our data mainly identified neuronal processes inherent to patients suffering from predominantly negative symptomatology which was the group the most distinguishable from both, the healthy controls and the positive symptomatic group in local neuronal processing (see group effects in ACC gamma and right BA40 theta). That this group stands out is not surprising given that the two patient groups only differ significantly in the negative symptoms (see **Table 1**) while their positive symptomatology scores are not significantly different. The fact that the performance between groups was not different points toward the aberrant neuronal processing displayed by the negative symptomatic group really being partly of a compensatory nature; however, from our data we cannot make any definite conclusions about the meaning of different oscillatory patterns or suggestions regarding causality. Given that aberrant gamma oscillations are linked to a dysregulation of GABAergic inhibitory neurotransmission, the differential findings in the gamma frequency band between the two patient groups might have potential implications for medication treatment of the SZ subgroups in the future.

We argue that the set of results might have very distinct origins and functions. The pattern of dysconnectivity in SZ which we also found in this study might be explained by general white matter loss in patients (e.g., Roalf et al., 2015), irrespective of symptomatology. However, diffusion tensor imaging studies would be needed to confirm such a claim. With regards to the local effects we found in right parietal and ACC theta power and frontal gamma power, this might reflect either on local disruptions (in the case of parietal theta activity) or alternatively, compensatory mechanisms in order to counter processing deficits. The increased frontal gamma and theta activity in the negative symptomatic group and positive symptomatic group, respectively, fits nicely with findings suggesting an increase in frontal activity as compensatory mechanism (i.e., hyperfrontality) as gamma activity has been found to reflect local neuronal spiking and frontal theta activity is strongly linked to executive functions.

It is important to emphasize that the above findings are unlikely to represent only dysfunctional neural processes. Disruption of a neural network may also trigger compensatory mechanisms. Thus, in particular the here described local differences between SZ patients and healthy controls, as well as, between the negative and positive symptomatic patient groups can represent local disruption or local compensation mechanisms. Considering that the negative and positive patient groups' behavioral performance was at the level of the healthy controls, the presence of such compensatory mechanisms is more than likely. However, it is also important to note that in the present study the healthy control sample was a tight match to the patient sample. While most studies comparing SZ patients and healthy controls report that patients perform markedly worse than healthy controls, the non-existent group difference in our study might indicate that no other factors (e.g., general cognitive abilities) contributed to the differences in brain oscillatory activity we found.

Furthermore, it is relevant to point out that the negative and positive patient groups received various psychopharmacological medications, which could potentially influence oscillatory processes; especially as there was a significant difference between the two patient groups. Hence it cannot be excluded that our results may be affected by these medications. However, the impact of medications on oscillatory processes is most likely generic and not task-specific. The presented results were specific to executive functions in a working memory task and do not reflect on generally altered oscillatory patterns as investigated in studies looking at resting EEG activity. It might also be worth mentioning that during the baseline period in our task there was no significant difference in either frequency band between groups. Moreover, it was found that prefrontal theta and gamma changes are not associated with psychopharmacological treatment in first-episode SZ patients (e.g., Minzenberg et al., 2010) and that deficits are not just due to lack of concentration, distracting positive symptoms or medication effects (e.g., Kraguljac et al., 2013).

Finally, we want to highlight that our analysis was strictly hypothesis driven. That is we did only analyse regions and frequency bands that are strongly implicated in fronto-parietal executive functions and visual working memory operations that are easily accessible with EEG source localization; i.e., the ACC and BA40. We cannot exclude, however, that other regions might play an important role and show distinct patterns in patients and controls, and more to the point, between the two patient groups. This would need to be further investigated with a more exploratory approach and potentially wider range of cognitive tasks and neuroimaging methods. In addition, in order to be able to make definite claims our results would need to be investigated further with a much larger sample of patients and healthy controls.

CONCLUSION

In conclusion, our results indicate that indeed, the fronto-parietal executive functions network as indexed by theta phase synchronization is comprised in SZ. Moreover, local frontal and right parietal activity in the theta and gamma frequency ranges can distinguish between patients with predominantly negative and predominantly positive symptomatology; and are especially able to differentiate patients with negative symptomatology from patients with positive symptoms and healthy controls. Finally, task-related theta and gamma oscillations can be highly beneficial for understanding the multifaceted nature of SZ and how its various cognitive dysfunctions and symptoms emerge—even in the absence of behavioral impairment—and so in furthering its treatment.

AUTHOR CONTRIBUTIONS

BB and TM share the first authorship for this paper and contributed equally. BB, data collection, data analysis, writing manuscript; TM, data analysis, writing manuscript; BG, implementation of experiment, data collection, writing manuscript; RS, WA, implementation of experiment, writing manuscript; PS, implementation of experiment, data analysis, writing manuscript.

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REFERENCES

Basar-Eroglu, C., Brand, A., Hildebrandt, H., Kedzior, K. K., Mathes, B., and Schmiedt, C. (2007). Working memory related gamma oscillations in schizophrenia patients. *Int. J. Psychophysiol.* 64, 39–45. doi: 10.1016/j.ijpsycho.2006.07.007

Berger, B., Omer, S., Minarik, T., Sterr, A., and Sauseng, P. (2014). Interacting memory systems – does EEG alpha activity respond to semantic long-term memory access in a working memory task? *Biology* 4, 1–16. doi: 10.3390/biology4010001

Buzsaki, G., and Wang, X.-J. (2012). Mechanisms of gamma oscillations. *Annu. Rev. Neurosci.* 35, 203–225. doi: 10.1146/annurev-neuro-062111-150444

Callicott, J. H., Mattay, V. S., Verchinski, B. A., Marenco, S., Egan, M. F., and Weinberger, D. R. (2003). Complexity of prefrontal cortical dysfunction in schizophrenia: More than up or down. *Am. J. Psychiatry* 160, 2209–2215. doi: 10.1176/appi.ajp.160.12.2209

Carter, C. S., Mintun, M., Nichols, T., and Cohen, J. D. (1997). Anterior cingulate gyrus dysfunction and selectrive attentino deficit in schizophrenia: [15 O]H2O PET study during single-trial stroop task performance. *Am. J. Psychiatry* 154, 1670–1675. doi: 10.1176/ajp.154.12.1670

Cavanagh, J. G., and Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. *Trends Cogn. Sci.* 18, 414–421. doi: 10.1016/j.tics.2014.04.012

Cho, R. Y., Konecky, R. O., and Carter, C. S. (2006). Impairments in frontal cortical γ synchrony and cognitive control in schizophrenia. *Proc. Natl. Acad. Sci. U.S.A.* 103, 19878–19883. doi: 10.1073/pnas.0609440103

Cohen, M. X., and Ridderinkhof, K. R. (2013). EEG source reconstruction reveals frontal-parietal dynamics of spatial conflict processing. *PLoS ONE* 8:e57293. doi: 10.1371/journal.pone.0057293

Cowan, N., Li, D., Moffitt, A., Becker, T. M., Martin, E. A., Saults, J. S., et al. (2011). A neural region of abstract working memory. *J. Cogn. Neurosci.* 23, 2852–2863. doi: 10.1162/jocn.2011.21625

Dasklakis, Z. J., Fitzgerald, P. B., and Christensen, B. K. (2007). The role of cortical inhibition in the pathophysiology and treatment of schizophrenia. *Brain Res. Rev.* 56, 427–442. doi: 10.1016/j.brainresrev.2007.09.006

Etkin, A., Gyurak, A., and O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues Clin. Neurosci.* 15, 419–429.

Ettinger, U., Mohr, C., Gooding, D. C., Cohen, A. S., Rapp, A., Haenschel, C., et al. (2015). Cognition and brain function in schizotypy: a selective review. *Schizophr. Bull.* 41, 417–426. doi: 10.1093/schbul/sbu190

Franke, G. H. (2000). *BSI. Brief Symptom Inventory von L. R. Derogatis Deutsche Version*. Göttingen: Beltz.

Gandal, M. J., Edgar, J. C., Klook, K., and Siegel, S. J. (2012). Gamma synchrony: towards a translational biomarker for the treatment resistant symptoms of schizophrenia. *Neuropharmacology* 62, 1504–1518. doi: 10.1016/j.neuropharm.2011.02.007

Gevins, A., Smith, M. E., McEvoy, L., and Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. *Cereb. Cortex* 7, 374–385. doi: 10.1093/cercor/7.4.374

Glahn, D. D., Ragland, J. D., Abramoff, A., Barrett, J., Laird, A. R., Bearden, C. E., et al. (2005). Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum. Brain Mapp.* 25, 60–69. doi: 10.1002/hbm.20138

Griesmayr, B., Berger, B., Stelzig-Schoeler, R., Aichhorn, W., Bergmann, J., and Sauseng, P. (2014). EEG theta phase coupling during executive control of visual working memory investigated in individuals with schizophrenia and in healthy controls. *Cogn. Affect. Behav. Neurosci.* 14, 1340–1355. doi: 10.3758/s13415-014-0272-0

Haenschel, C., Bittner, R. A., Waltz, J., Haertling, F., Wibral, M., Singer, W., et al. (2009). Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *J. Neurosci.* 29, 9481–9489. doi: 10.1523/JNEUROSCI.1428-09.2009

Haenschel, C., and Linden, D. (2011). Exploring intermediate phenotypes with EEG: working memory dysfunction in schizophrenia. *Behav. Brain Res.* 216, 481–495. doi: 10.1016/j.bbr.2010.08.045

Herrmann, C. S., and Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clin. Neurophysiol.* 116, 2719–2733. doi: 10.1016/j.clinph.2005.07.007

Huhlshoff Pol, H. E., Schnack, H. G., Bertens, M. G., van Haren, N. E., van der Tweel, I., Staal, W. G. et al. (2002). Volume changes in gray matter in patients with schizophrenia. *Am. J. Psychiatry* 159, 244–250. doi: 10.1176/appi.ajp.159.2.244

Ishii, R., Canuet, L., Ishihara, T., Aoki, Y., Ikeda, S., Hata, M., et al. (2014). Frontal midline theta rhythm and gamma power changes during focused attention on mental calculation: an MEG beamformer analysis. *Front. Hum. Neurosci.* 8:406. doi: 10.3389/fnhum.2014.00406

Jackson, M. C., Morgan, H. M., Shapiro, K. L., Mohr, H., and Linden, D. E. J. (2011). Strategic resource allocation in the human brain supports cognitive coordination of object and spatial working memory. *Hum. Brain Mapp.* 32, 1330–1348. doi: 10.1002/hbm.21112

Karlsgodt, K. H., Glahn, D. C., van Erp, T. G. M., Therman, S., Huttunen, M., Manninen, M., et al. (2007). The relationship between performance and fMRI signal during working memory in patients with schizophrenia, unaffected co-twins, and control subjects. *Schizophr. Res.* 89, 191–197. doi: 10.1016/j.schres.2006.08.016

Kay, S. R., Fiszbein, A., and Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276. doi: 10.1093/schbul/13.2.261

Kerns, J. G., Cohen, J. D., MacDonald, A. W. III, Johnson, M. K., Stenger, V. A., Aizenstein, H., et al. (2005). Decreased conflict- and error-related activity in the

anterior cingulate cortex in subjects with schizophrenia. *Am. J. Psychiatry* 162, 1833–1839. doi: 10.1176/appi.ajp.162.10.1833

Kiriakopoulos, M., Bargiotas, T., Barker, G. J., and Frangou, S. (2008). Diffusion tensor imaging in schizophrenia. *Eur. Psychiatry* 23, 255–273. doi: 10.1016/j.eurpsy.2007.12.004

Koychev, I., El-Deredy, W., Mukherjee, T., Haenschel, C., and Deakin, J. F. W. (2012). Core dysfunction in schizophrenia: electrophysiology trait biomarkers. *Acta Psychiatr. Scand.* 126, 59–71. doi: 10.1111/j.1600-0447.2012.01849.x

Kraguljac, N. V., Srivastava, A., and Lahti, A. C. (2013). Memory deficits in schizophrenia: a selective review of functional magnetic resonance imaging (FMRI) studies. *Behav. Sci. (Basel)* 3, 330–347. doi: 10.3390/bs3030330

Lachaux, J.-P., Rodriguez, E., Martinerie, J., and Varela, F. J. (1999). Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* 8, 194–208.

Lisman, J. (2012). Excitation, inhibition, local oscillations, or large-scale loops: what causes the symptoms of schizophrenia? *Curr. Opin. Neurobiol.* 22, 537–544. doi: 10.1016/j.conb.2011.10.018

Lisman, J., and Buzsaki, G. (2008). A neural coding scheme formed by the combined function of gamma and theta oscillations. *Schizophr. Bull.* 34, 974–980. doi: 10.1093/schbul/sbn060

Majerus, S., D'Argembeau, A., Perez, T. M., Belayachi, S., van der Linden, M., Collette, F., et al. (2010). The commonality of neural networks of verbal and visual short-term memory. *J. Cogn. Neurosci.* 22, 2570–2593. doi: 10.1162/jocn.2009.21378

Malhotra, P., Coulthard, E. J., and Husain, M. (2009). Role of right posterior parietal cortex in maintaining attention to spatial locations over time. *Brain* 132, 645–660. doi: 10.1093/brain/awn350

Manoach, D. S. (2003). Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr. Res.* 60, 285–298. doi: 10.1016/S0920-9964(02)00294-3

Manoach, D. S., Gollub, R. L., Benson, E. S., Searl, M. M., Goff, D. C., Halpern, E., et al. (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biol. Psychiatry* 48, 99–109. doi: 10.1016/S0006-3223(00)00227-4

Meyer-Lindenberg, A., Poline, J. B., Kohn, P. D., Holt, J. L., Egan, M. F., Weinberger, D. R., et al. (2001). Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *Am. J. Psychiatry* 158, 1809–1817. doi: 10.1176/appi.ajp.158.11.1809

Minzenberg, M. J., Firl, A. J., Yoon, J. H., Gomes, G. C., Reinking, C., and Carter, C. S. (2010). Gamma oscillatory power is impaired during cognitive control independent of medication status in first-episode schizophrenia. *Neuropsychopharmacology* 35, 2590–2599. doi: 10.1038/npp.2010.150

Mitchell, D. J., McNaughton, N., Flanagan, D., and Kirk, I. J. (2008). Frontal-midline theta from the perspective of hippocampal "theta". *Prog. Neurobiol.* 86, 156–185. doi: 10.1016/j.pneurobio.2008.09.005

Mizuhara, H., and Yamagutchi, Y. (2007). Human cortical circuits for central executive function emerge by theta phase synchronization. *Neuroimage* 36, 232–244. doi: 10.1016/j.neuroimage.2007.02.026

Möller, H.-J., Müller, W. E., and Volz, H.-P. (2000). *Psychopharmakotherapie. Ein Leitfaden für Klinik und Praxis*. Stuttgart: Kohlhammer.

Moran, L. V., and Hong, L. E. (2011). High vs low frequency neural oscillations in schizophrenia. *Schizophr. Bull.* 37, 659–663. doi: 10.1093/schbul/sbr056

Moran, R. J., Campo, P., Maestu, F., Reilly, R. B., Dolan, R. J., and Strange, B. A. (2010). Peak frequency in the theta and alpha bands correlates with human working memory capacity. *Front. Hum. Neurosci.* 4:200. doi: 10.3389/fnhum.2010.00200

Moscovitch, M., Kapur, S., Köhler, S., and Houle, S. (1995). Distinct neural correlates of visual long-term memory for spatial location and object identity: a positron emission tomography study in humans. *Proc. Natl. Acad. Sci. U.S.A.* 92, 3721–3725. doi: 10.1073/pnas.92.9.3721

O'Keefe, J., and Recce, M. L. (1993). Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330. doi: 10.1002/hipo.450030307

Oleksiak, A., Postma, A., van der Ham, I. J., Klink, P. C., and van Wezel, R. J. (2011). A review of lateralization of spatial functioning in nonhuman primates. *Brain Res. Rev.* 67, 56–72. doi: 10.1016/j.brainresrev.2010.11.002

Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., and Jensen, O. (2006). Theta and gamma oscillations predict encoding and retrieval of declarative memory. *J. Neurosci.* 26, 7523–7531. doi: 10.1523/JNEUROSCI.1948-06.2006

Pascual-Marqui, R. D., Michel, C. M., and Lehmann, D. (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int. J. Psychophysiol.* 18, 49–65. doi: 10.1016/0167-8760(84)90014-X

Pisella, L. (2016). Visual perception is dependent on visuospatial working memory and thus on the posterior parietal cortex. *Ann. Phys. Rehabil. Med.* doi: 10.1016/j.rehab.2016.01.002. [Epub ahead of print].

Pisella, L., Alahyane, N., Blangero, A., Thery, F., Blanc, S., and Pelisson, D. (2011). Right-hemispheric dominance for visual remapping in humans. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 366, 572–585. doi: 10.1098/rstb.2010.0258

Popov, T., Wienbruch, C., Meissner, S., Miller, G. A., and Rockstroh, B. (2015). A mechanism of deficient interregional neural communication in schizophrenia. *Psychophysiology* 52, 648–656. doi: 10.1111/psyp.12393

Roalf, D. R., Gur, R. E., Verma, R., Parker, W. W., Quarmley, M., Ruparel, K., et al. (2015). White matter microstructure in schizophrenia: Associations to neurocognitive and clinical symptomatology. *Schizophr. Res.* 161, 42–49. doi: 10.1016/j.schres.2014.09.026

Rogasch, N. C., Daskalakis, Z. J., and Fitzgerald, P. B. (2014). Cortical inhibition, excitation, and connectivity in schizophrenia: a review of insights from transcranial magnetic stimulation. *Schizophr. Bull.* 40, 685–696. doi: 10.1093/schbul/sbt078

Romei, V., Driver, J., Schyns, P. G., and Thut, G. (2011). Rhythmic TMS over right parietal cortex causally links distinct brain frequencies to global visual processing. *Curr. Biol.* 21, 334–337. doi: 10.1016/j.cub.2011.01.035

Roux, F., and Uhlhaas, P. J. (2014). Working memory and neural oscillations: alpha-gamma versus theta-gamma codes for distinct WM information? *Trends Cogn. Sci.* 18, 16–25. doi: 10.1016/j.tics.2013.10.010

Sauseng, P., Griesmayr, B., Freunberrger, R., and Klimesch, W. (2010). Control mechansims in working memory: A possible function of EEG theta oscillations. *Neurosci. Biobehav. Rev.* 34, 1015–1022. doi: 10.1016/j.neubiorev.2009.12.006

Sauseng, P., Hoppe, J., Klimesch, W., Gerloff, C., and Hummel, F. C. (2007). Dissociation of sustained attention from central executive functions: local activity and interregional connectivity in the theta range. *Eur. J. Neurosci.* 25, 587–593. doi: 10.1111/j.1460-9568.2006.05286.x

Sauseng, P., Klimesch, W., Gruber, W., and Birbaumer, N. (2008). Cross-frequency phase synchronization: a brain mechanism of memory matching and attention. *Neuroimage* 40, 308–317. doi: 10.1016/j.neuroimage.2007.11.032

Sauseng, P., Klimesch, W., Schabus, M., and Doppelmayr, M. (2005). Fronto-parietal EEG coherence in theta and upper alpha reflect central executive functions of working memory. *Int. J. Psychophysiol.* 57, 97–703. doi: 10.1016/j.ijpsycho.2005.03.018

Schmitt, A., Hasan, A., Gruber, O., and Falkai, P. (2011). Schizophrenia is a disorder or disconnectivity. *Eur. Arch. Psychiatry* 261, s150–s154. doi: 10.1007/s00406-011-0242-2

Senkowski, D., and Gallinat, J. (2015). Dysfunctional prefrontal gamma-band oscillations reflect working memory and other cognitive deficits in schizophrenia. *Biol. Psychiatry* 77, 1010–1019. doi: 10.1016/j.biopsych.2015.02.034

Singer, W., and Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* 18, 555–586. doi: 10.1146/annurev.ne.18.030195.003011

Smith, E. E., Jonides, J., and Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cereb. Cortex* 6, 11–20. doi: 10.1093/cercor/6.1.11

Teffer, K., and Semendeferi, K. (2012). Human prefrontal cortex: evolution, development, and pathology. *Prog. Brain Res.* 195, 191–218. doi: 10.1016/B978-0-444-53860-4.00009-X

Tsujimoto, T., Shimazu, H., and Isomura, Y. (2006). Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices. *J. Neurophysiol.* 95, 2987–3000. doi: 10.1152/jn.00730.2005

Uhlhaas, P. J., and Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* 11, 100–113. doi: 10.1038/nrn2774

Uhlhaas, P. J., and Singer, W. (2014). Oscillations and neuronal dynamics in schizophrenia: the search for basic symptoms and translational opportunities. *Biol. Psychiatry* 77, 1001–1009. doi: 10.1016/j.biopsych.2014.11.019

Uhlhaas, P. J., and Singer, W. (2015). Oscillations and neuronal dynamics in schizophrenia: the search for basic symptoms and translational opportunities. *Biol. Psychiatry* 77, 1001–1009. doi: 10.1016/j.biopsych.2014.11.019

van Erp, T. G. M., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, D., Andreassen, O. A., et al. (2015). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol. Psychiatry* 2015, 1–7. doi: 10.1038/mp.2015.63

Voytek, B., and Knight, R. T. (2015). Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biol. Psychiatry* 77, 1089–1097. doi: 10.1016/j.biopsych,.2015.04.016

Wang, L., Liu, X., Guise, K. G., Knight, R., Ghajar, J., and Fan, J. (2009). Effective connectivity of the fronto-parietal network during attention control. *J. Cogn. Neurosci.* 22, 543–553. doi: 10.1162/jocn.2009.21210

Wen, W., Yong, H., and Sachdev, P. (2011). Structural brain networks and neuropsychiatric disorders. *Curr. Opin. Psychiatry* 24, 219–225. doi: 10.1097/YCO.0b013e32834591f8

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J. Clin. Psychiatry* 64, 663–667. doi: 10.4088/JCP.v64n0607

Wu, X., Chen, X., Li, Z., Han, S., and Zhang, D. (2007). Binding of verbal and spatial information in human working memory involves large-scale neural synchronization at theta frequency. *Neuroimage* 35, 1654–1662. doi: 10.1016/j.neuroimage.2007.02.011

Zhou, Y., Fan, L., Qiu, C., and Jiang, T. (2015). Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia. *Neurosci. Bull.* 31, 207–219. doi: 10.1007/s12264-014-1502-8

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REVIEW
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Executive Dysfunctions: The Role in Attention Deficit Hyperactivity and Post-traumatic Stress Neuropsychiatric Disorders

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Executive functions (EFs) is an umbrella term for various cognitive processes controlled by a complex neural activity, which allow the production of different types of behaviors seeking to achieve specific objectives, one of them being inhibitory control. There is a wide consensus that clinical and behavioral alterations associated with EF, such as inhibitory control, are present in various neuropsychiatric disorders. This paper reviews the research literature on the relationship between executive dysfunction, frontal-subcortical neural circuit changes, and the psychopathological processes associated with attention deficit hyperactivity disorder (ADHD) and post-traumatic stress disorder (PTSD). A revision on the role of frontal-subcortical neural circuits and their presumable abnormal functioning and the high frequency of neuropsychiatric symptoms could explain the difficulties with putting effector mechanisms into action, giving individuals the necessary tools to act efficiently in their environment. Although, neuronal substrate data about ADHD and PTSD has been reported in the literature, it is isolated. Therefore, this review highlights the overlapping of neural substrates in the symptomatology of ADHD and PTSD disorders concerning EFs, especially in the inhibitory component. Thus, the changes related to impaired EF that accompany disorders like ADHD and PTSD could be explained by disturbances that have a direct or indirect impact on the functioning of these loops. Initially, the theoretical model of EF according to current neuropsychology will be presented, focusing on the inhibitory component. In a second stage, this component will be analyzed for each of the disorders of interest, considering the clinical aspects, the etiology and the neurobiological basis. Additionally, commonalities between the two neuropsychiatric conditions will be taken into consideration from the perspectives of cognitive and emotional inhibition. Finally, the implications and future prospects for research and interventions in the area will be outlined, with the intention of contributing scientific reference information that encompasses the knowledge and understanding of executive dysfunction and its relationship with these treated disorders.

Keywords: ADHD, executive functions, inhibitory control, neuropsychiatric disorders, PTSD

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INTRODUCTION

General Aspects of Executive Functions

Executive functions (EFs), also known as executive control or cognitive control, are a complex set of interrelated cognitive processes controlled by its top–down nature (Diamond, 2013) and mediated by dynamic behaviors in order to achieve goal-oriented behaviors that are essential for an individual to solve problems, resist interference, hold attention, learn, make decisions, plan, and regulate their behavior (including in new situations), among other skills necessary for everyday life (Diamond, 2013; Chung et al., 2014).

In the historical background, it has been found that although the term "EFs" was coined by Lezak, it was Luria – his direct predecessor – who first described it, even without mentioning it directly. He proposed a brain functioning model based on clinical findings, which consists of three functional units: (1) motivation arousal (reticular and limbic systems); (2) acquisition, processing, and storage of information (post-rolandic cortical areas); and (3) programming, monitoring, and verification of behavior [dependent on the activity of the prefrontal cortex (PFC); Ardila, 2008]. This complex brain system would be mediated by neuroanatomical and functional hierarchical regions, and would work together to regulate all behavior and mental processes (Jurado and Rosselli, 2007).

Regarding the classification of EFs, inhibition can be highlighted (inhibitory control, including self – behavioral inhibition – and control of interference, selective attention and cognitive inhibition), as well as working memory (WM), cognitive flexibility (also known as mental flexibility; Miyake et al., 2000), reasoning, problem solving, and planning (Collins and Koechlin, 2012; Lunt et al., 2012).

Fuster (2008) was one of the most recognized in the EFs study and was the one who proposed a general theory of the PFC and ideas about the importance of this area in the temporal structure of behavior. He suggested that EFs are cognitive skills that enable the organization of a sequence of actions in pursuit of a goal, and proposed the following cognitive skills as part of EFs: attention (alert, set, spatial attention, sustained attention, and control interference), memory, WM, planning, temporal integration, decision making, and inhibitory control.

Recently, there has been a consensus that three basic nuclei compose EFs: WM, cognitive flexibility, and inhibition of prepotent impulses (Hofmann et al., 2012; Diamond, 2013). WM refers to temporary maintenance and active control of information, avoiding distraction (Kane et al., 2001). For its part, cognitive flexibility is the ability to change and modify the course of thoughts or actions to multiple tasks that require it (Elliott, 2003), and inhibition is the ability to inhibit dominant or automatic responses when is necessary (Miyake et al., 2000). See **Figure 1**.

The focus of this study(revision) will be inhibitory control in EFs, describing and expanding its general characteristics, and the neuropsychiatric conditions of attention deficit hyperactivity disorder (ADHD) and post-traumatic stress disorder (PTSD), with special emphasis on cognitive and emotional perspectives. This paper reviews the research literature on the relationship between executive dysfunction, frontal-subcortical neural circuit changes, and psychopathological processes associated with ADHD and PTSD.

Neuroanatomy of Executive Functions

Executive Functions are closely linked to the activity of the frontal lobes, which establish a significant correlation on a clinical-anatomical level regarding clear evidence from case reports of patients with difficulties that arise after brain injuries to frontal areas, and which result in alterations called "executive dysfunction" or "frontal lobe dysfunction" (Elliott, 2003). But recently, with the advance of technology, various imaging methods [such as magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and Positron emission tomography (PET)] there is evidence that executive functioning is associated with several distributed networks (Chung et al., 2014), which include not only the frontal regions of the cortex but the subcortical areas too (Collette et al., 2006; Bonelli and Cummings, 2007; Jurado and Rosselli, 2007; Marvel and Desmond, 2010).

The frontal lobe is anatomically shaped, in both human and non-human primates, by the dorsolateral PFC, the medial and cingulate PFC, and the orbital PFC (Fuster, 2002). These areas are involved in complex cognitive processes; the dorsolateral region in WM, the anterior and medial areas in desire and motivation, and the orbital region in inhibitory impulse control and interference (Fuster, 2002). See **Figure 2**.

Some authors have emphasized the "circuits," specifically the frontal-subcortical circuits, claiming that the dorsolateral prefrontal circuit is involved in the organization of information to facilitate a response; the anterior cingulate circuit is related to the conduct of motivation; and orbitofrontal circuit translates the limbic and emotional information into behavioral responses. For these authors, the deterioration of EFs resulting in apathy and impulsivity, for example, is a sign of dysfunction of the frontal-subcortical circuit (Bonelli and Cummings, 2007). Additionally, it is important to mention that the EFs, although closely linked with the PFC, do not rely only on this structure, but also on the intact functioning of the cortical-striatal dopaminergic system (Elliott, 2003). It is the neurobiological basis of EFs, occupying a favored place for "orchestrating all of these functions," as it has the ability to receive and send information to almost all sensory and motor brain systems (Arnsten and Li, 2005).

Bonelli and Cummings (2007) reported that neuropsychiatric expressions associated with neurodegenerative diseases are closely linked to impairments in neurocircuits generated from frontal connections with other brain areas, especially subcortical areas, since the effector mechanisms allowing the organism to act efficiently within its environment are disturbed. This supports the link that has been found between faiths and different psychopathological and behavioral disorders (Närhi et al., 2010; Biederman et al., 2011).

According to Jurado and Rosselli (2007) there are numerous neurodevelopmental and adult disorders for which alterations to the EFs have been identified, linked to the symptoms also

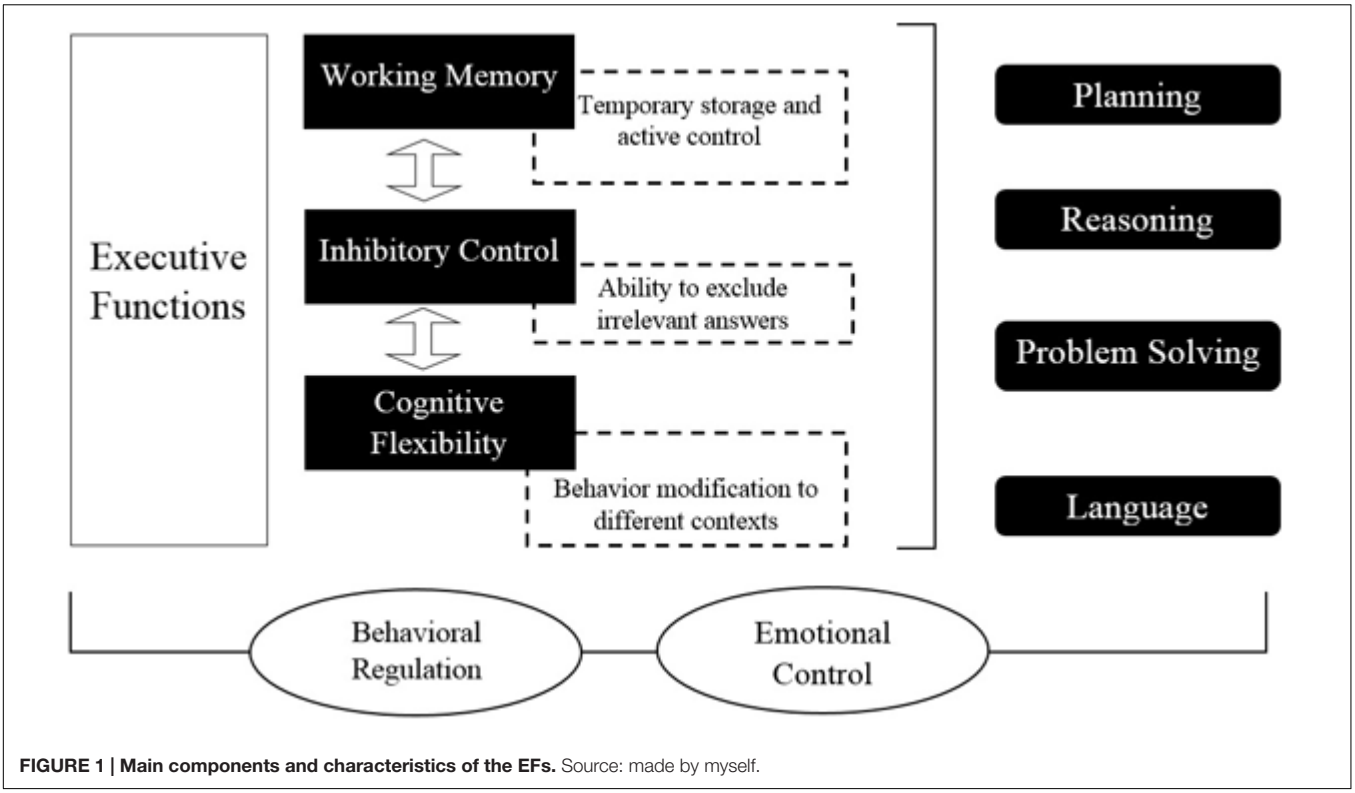

FIGURE 1 | Main components and characteristics of the EFs. Source: made by myself.

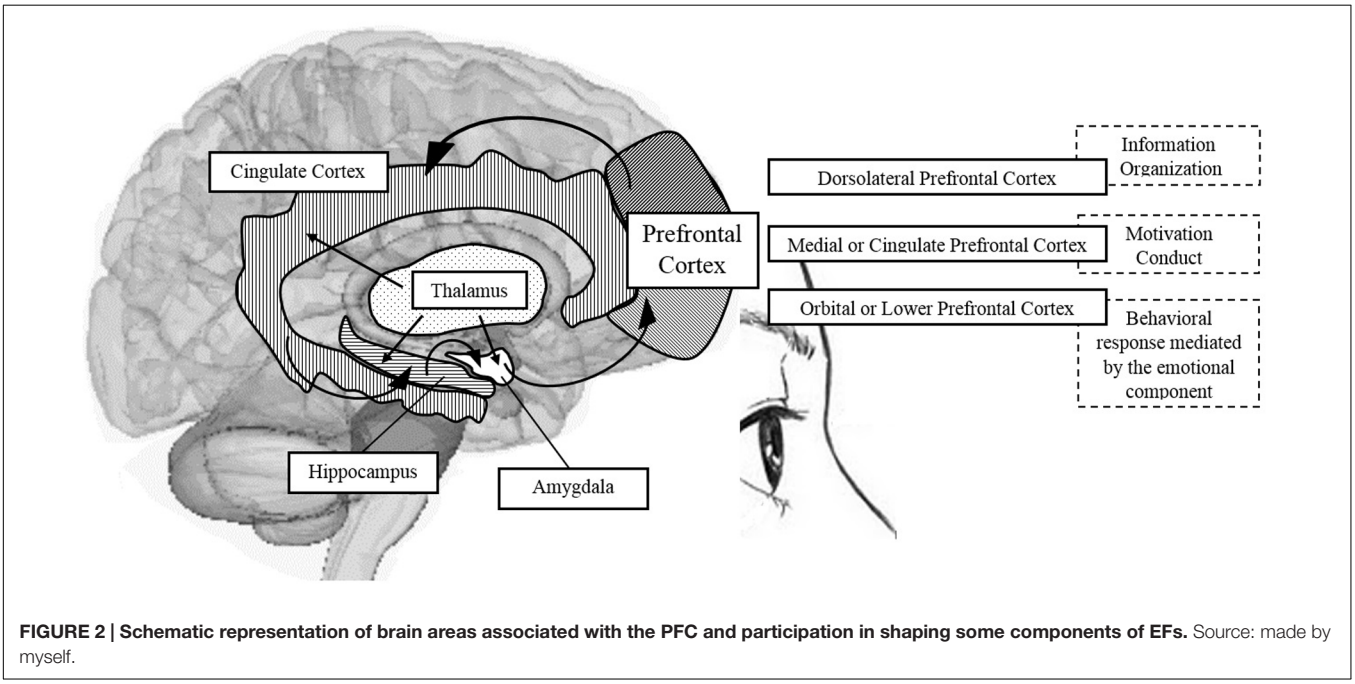

FIGURE 2 | Schematic representation of brain areas associated with the PFC and participation in shaping some components of EFs. Source: made by myself.

found in people with damaged frontal lobes, such as sustained and selective attention, impulsivity, hyperactivity, and deficits in warning systems, WM, the three mechanisms of inhibitory control (waiting, impulse, or interference control) and self-regulation of behavior, as well as perseveration, cognitive rigidity and planning difficulties, among others.

Inhibitory Control

Inhibitory control is considered an important EF due to its ability to control attention, behavior, thoughts and/or emotions, in order to override a strong internal or external predisposition to distraction, and to do so whenever appropriate or necessary according to the demands of the environment. The term

"inhibition" refers to several different types of inhibition, such as response or motor inhibition, cognitive inhibition, interference control, motivational inhibition, and the automatic inhibition of attention (Diamond, 2013).

Inhibitory control refers to the mental processes responsible for intentional and voluntary control, involving the ability to resist interferences from irrelevant information and to erase previously relevant information that may create incentives in the short term, but that are not functional to solving a particular problem (Carlson and Wang, 2007). Motor inhibition is defined as the individual's ability to inhibit a behavioral response to a stimulus, i.e., the ability to inhibit a strong behavioral tendency (Diamond, 2006). On the other hand, cognitive inhibition refers to the suppression of irrelevant information in WM (Miyake et al., 2000). It has been found that failures in cognitive inhibition are associated with internalizing problems; on the contrary, the failures are related to behavioral inhibition outsourcing the problems and are based on the individual's ability to inhibit the behavioral response to a stimulus, specifically in tasks that require setting a plan and eliminating wrong answers (Diamond, 2013).

The existence of multiple inhibition types suggests the probability of an overlap between the different brain regions that underlie these inhibitory processes (Collette et al., 2001).

It is argued that the neural substrate of inhibitory control lies mainly in dorsolateral, orbitofrontal and ventromedial areas of the PFC (Fuster, 2002; Ditye et al., 2012), associated with the right prefrontal gyrus (Ditye et al., 2012). Thus, interactions between the right PFC, the basal ganglia, the primary motor regions and the medial temporal lobe are important for the expression of inhibitory control (Aron et al., 2004).

Neuroimaging studies that address inhibition processes have shown the involvement of several regions in the cingulate, prefrontal, parietal, and temporal areas (Collette et al., 2001). However, the exact role of the regions associated with inhibition processes is not completely defined, because the regions mentioned are quite heterogeneous (Collette et al., 2006). Some neuropsychiatric disorders are closely linked to defects in frontal-subcortical neurocircuits. These circuits participate in a variety of neuropsychiatric disorders such as Tourette's syndrome, Huntington's disease, obsessive-compulsive disorder, ADHD, schizophrenia and mood disorders, which occur as a result of changes in the orbitofrontal circuit and therefore in inhibitory control (Bonelli and Cummings, 2007).

ATTENTION DEFICIT DISORDER/HYPERACTIVITY

Characteristics, Prevalence, Diagnostic Criteria, and Comorbidity

Attention deficit hyperactivity disorder is one of the most common problems that develop during neurodevelopmental childhood, considered a disturbance and prevalent in approximately 5% of children and 2.5% of adults (American Psychiatric Association [APA], 2013).

According to several studies, it is estimated that up to 67% of these children will ontinue to exhibit symptoms in adulthood (Lundervold et al., 2011; Ranby et al., 2012). However, the prevalence data reported in the literature varies due to the range of diagnostic criteria and assessment methods used in the studies. With regard to symptoms, Sobanski et al. (2010) have postulated that hyperactivity behavior tends to decrease with age, while inattention increases.

Adolescents and adults with ADHD have a higher risk of failure in school, emotional problems, difficulties in social relationships and sometimes trouble with the law.

The American Psychiatric Association [APA] (2013) argues that many parents first observe excessive motor activity when the child is in early childhood, with symptoms that are difficult to distinguish from normal behavior, which can be variables before 4 years of age. Furthermore, ADHD is often identified at school when inattention becomes more pronounced and affects performance, stabilizing during early adolescence, but possibly worsening with the onset of antisocial behavior. Even so, for most individuals with ADHD the symptoms of motor hyperactivity become less noticeable during adolescence or adulthood, but difficulties associated with restlessness, inattention, planning and impulsivity may persist.

According to the American Psychiatric Association [APA] (2013) in its Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ADHD is defined as a persistent pattern of behavior that manifests itself in various contexts (school/work, home, social, etc.) that interferes significantly with the development and functioning of the individual with the disorder. Thus, the APA states that the symptoms fall into two major predominant areas: inattention, and hyperactivity and impulsivity. Inattention manifests behaviorally with deviations at work, lack of persistence, difficulty maintaining attention, and disorganization, which are not due to a challenge or a lack of understanding; hyperactivity is reflected in excessive motor activity when it is not adequate; and impulsivity is evidenced by hasty actions that are taken without reflection, resulting from a desire for immediate reward or an inability to delay gratification. These characteristics are reflected in the established diagnostic criteria. See **Table 1**.

Regarding the diagnosis of ADHD, Arnett et al. (2013) believe that it must be mainly clinical, as there is no additional examination or neurobiological sign itself that is final; so it must be established based on clinical symptoms. Confirmation via questionnaires, neuropsychological tests and neuropsychological studies is needed for these patients, especially if they are validated by specific neuropsychological batteries that allow reassessments to control the patient's development regarding the indicated treatment.

It has been found that according to clinical research and the discussion in the DSM-5 (American Psychiatric Association [APA], 2013), comorbid disorders are common in individuals with ADHD. For example, oppositional defiant disorder coincides with ADHD in about half of children with combined prevalence and in about a quarter of predominantly inattentive children and adolescents; conduct disorder occurs in about a quarter of children and adolescents with combined

TABLE 1 | Summary of criteria and specific symptoms for the diagnosis of ADHD (American Psychiatric Association [APA], 2013).

Inattention	Hyperactivity/impulsivity
(1) Failure to pay attention to details or careless mistakes are made in schoolwork, work, or during other activities.	(1) Fidgets, claps hands or feet, or squirms in seat.
(2) Difficulty sustaining attention in tasks or recreational activities.	(2) Standing up in situations where they are expected to remain seated.
(3) Does not seem to listen when spoken to directly.	(3) Runs around or climbs in situations where it is not appropriate (may be limited to fidgeting in adolescents or adults).
(4) Does not follow instructions and fails to finish schoolwork, chores, or work duties.	(4) Is unable to play or engage in leisure activities quietly.
(5) Difficulty organizing tasks and activities	(5) Is "busy," acting as if impelled by a "motor."
(6) Avoids, dislikes, or lacks interest in starting tasks that require sustained mental effort.	(6) Talks excessively.
(7) Loses things necessary for tasks or activities.	(7) Responds unexpectedly or before a question has been concluded.
(8) Is easily distracted by external stimuli.	(8) Has difficulty taking turns.
(9) Forgets everyday activities.	(9) Disrupts or interferes with others (adolescents and adults may interfere or get ahead of what others are doing).
Combined	
Criteria for inattention (6+ symptoms) and hyperactivity-impulsivity (6+ symptoms) are met.	

The set of ADHD symptoms usually manifests before 12 years of age, presenting six or more of them (in older adolescents and adults aged 17 years of age, at least five symptoms are required) to diagnose any subtype of ADHD, maintained for a period exceeding 6 months, with an intensity that is incompatible with the level of development and has a direct negative impact on the social and academic/work activities of the individual.

presentation, depending on age and context; a lower percentage of children with ADHD have symptoms that meet criteria for disruptive mood dysregulation disorder; a specific learning disorder commonly occurs along with ADHD; anxiety disorders and major depressive disorders occur in a minority of individuals with ADHD, but more often than in the general population; intermittent explosive disorder occurs in a minority of adults with ADHD, but with levels above the general population; substance abuse disorders are present only in a minority of adults with ADHD, yet they are relatively more frequent among adults with ADHD than in the general population; and antisocial personality disorder and other personality disorders may be associated with ADHD in adults. Other disorders that may be comorbid with ADHD are obsessive-compulsive disorder, tic disorder and the autistic spectrum.

Cognitive Impairment in Attention Deficit Disorder/Hyperactivity

Attention deficit hyperactivity disorder has important cognitive consequences, especially in relation to EFs. Additionally, it is known that the disorder is not characterized by cognitive difficulties alone, but is also marked by an altered emotional level (recognition, regulation, and expression of emotions; Sobanski et al., 2010), a product of dysfunction in executive control processes; according to the DSM-5 (American Psychiatric Association [APA], 2013), this can generate a long-term impact on the operation and development of the individual.

The implications of ADHD, as well as being analyzed through measurements with neuropsychological and cognitive tests, is also studied using various neurological, neurophysiological and neuroimaging tests, with the electroencephalogram (EEG) having demonstrated its effectiveness. Recently, research related to the measurement of brain activity in individuals with ADHD showed a difference in activity patterns between children with and without ADHD, by evaluating electrophysiological variables such as reaction time (RT) in cognitive tasks (McLoughlin et al., 2014), in inhibitory control tasks (Bruckmann et al., 2012) and exposure to emotional stimuli (Singhal et al., 2012).

In general, the literature shows the existence of cognitive deficits in individuals with ADHD, such as deficits in attention, EFs, memory, and perception (Arnett et al., 2013). Thus, the deficit of individuals with ADHD, originated in dysfunction of the frontal lobes, specifically in the PFC, leading primarily to a delay or reduction of EFs, a basic prerequisite for the successful development of a variety of cognitive processes for achieving goals (Funahashi and Andreau, 2013).

A result of the alterations in the PFC, individuals with ADHD often have a syndrome associated with executive control disorders, mainly manifesting inhibitory difficulties in WM and planning (Willcutt et al., 2005), as well as productivity and creativity, and inability to abstract ideas and to anticipate the consequences of behavior, leading to increased impulsivity (Arnett et al., 2013); on the other hand, they also have significant difficulties modulating affective states and recognizing and understanding emotional information, which results in elevated levels of aggressiveness, irritability, or frustration (Martel and Nigg, 2006).

Neurobiology of Attention Deficit Disorder/Hyperactivity

Scientific studies demonstrate the involvement in ADHD of several neuroanatomical structures within the frontal cortex, especially the prefrontal area, the basal ganglia, and the posterior parietal cortex (Arnsten and Li, 2005).

Along with the PFC, the caudate nucleus and its associated circuitry play an important role in the pathogenesis of ADHD.

With MRI studies, structural abnormalities have been found in individuals with ADHD, related to reduced volumes of the left caudate nucleus and right anterior frontal cortex, indicating a reversal of the normal asymmetrical pattern. A bilateral reduction in the size of the putamen has also been found, as well as a reduction in the volume of the right globus pallidus (Cortese et al., 2012).

It is also known that through the use of neuroimaging techniques, structures such as the cerebellum show significantly lower measurements in children with ADHD (on average) throughout childhood and adolescence, compared with the same structures in children without the disorder; In addition, the right PFC is slightly larger in the general population, and its counterpart in the left hemisphere is more symmetrical in people with the disorder, affecting mental abilities such as inhibition of responses, planning behavior, selective focus and organization of information necessary for solving problems and using specific cognitive operations (memory, metacognition, learning, and reasoning; Doyle, 2006; Cortese et al., 2012). See **Figure 3**.

Studies using functional neuroimaging techniques with high spatial [single-photon emission computed tomography (SPECT), PET, and fMRI] temporal [event-related brain potentials (ERPs)] and spatiotemporal [magnetoencephalography (MEG)] resolutions show functional differences in the PFC and striatum in patients with ADHD compared to controls, indicating the existence of dysfunction in the frontostriatal network, which could explain the changes observed in processes such as response inhibition. Furthermore, they showed a decrease in gray matter in the frontal right turn and the rotation of the right posterior cingulate, and in the middle left white matter (Cortese et al., 2012).

Electroencephalogram studies show the existence of a relationship between clinical symptoms of ADHD and characteristics of brain activity, reporting the presence of increased theta activity in the EEG (Boutros et al., 2005).

Volkow et al. (2011) has also investigated the biochemical implications of ADHD, determining that the neurobiological basis of the disorder presents a dysfunction of dopaminergic, serotonergic and noradrenergic circuits, causing an alteration in some cognitive mechanisms. Castellanos (1997) proposed the unitary theory of dopamine transmission in ADHD, based on abnormalities in two dopaminergic regions: (a) hypoactivation cortical regions (anterior cingulate), which produces a cognitive deficit and (b) overactivity in subcortical regions (caudate nucleus), causing excessive motor levels.

Arnsten et al. (1996) suggested that there may be different abnormalities in two noradrenergic regions: an underactive cortical (dorsolateral prefrontal), which referred to primary care deficits (WM) and overactivity in the subcortical systems (locus coeruleus), resulting in over-alertness.

The genetic mechanisms of ADHD are polygenic and this study focused on those related to dopamine, a gene involved in ADHD that could be the D2 receptor gene located on chromosome 11 (11q22-23; Comings, 2001). Other associated genes include the transporter gene norepinephrine (NET1) and the dopamine receptor gene D1 (DRD1; Bobb et al., 2005).

In general, the various neurobiological implications of ADHD can explain and help to understand the effects that are mainly exhibited in cognitive processes, such as the EFs.

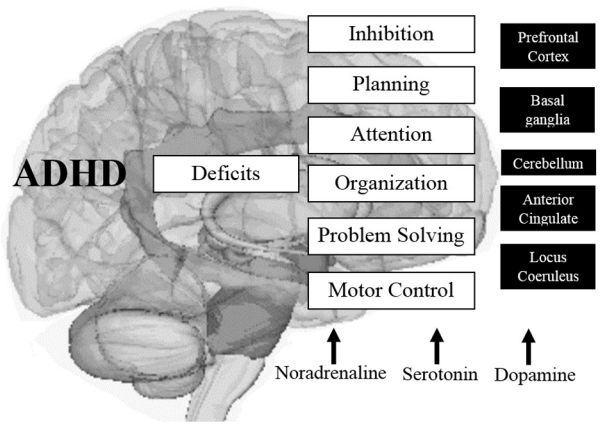

FIGURE 3 | Main altered brain structures in ADHD and their effects on cognitive components associated with EFs. Source: made by myself.

Inhibitory Control in Attention Deficit Disorder/Hyperactivity

One of the EFs most commonly affected in ADHD is inhibitory control (Doyle, 2006; Lange et al., 2010) and/or inability to inhibit responses associated with distracting stimuli (Arnsten and Li, 2005; Doyle, 2006).

Barkley (2006) argues that problems sustaining attention, such as ADHD, are the result of hypoactivity of the behavioral inhibition system, especially for poor interference control. He proposes a model (Barkley, 1997) in which he explains that the deficit in behavioral inhibition involves a delay or impairment in the development of four neuropsychological functions: the memory of non-verbal work, verbal WM, the self-regulation of emotion/motivation/activation, and reconstitution. The most important component of this model is the inhibition of behavior, which provides the basis for the neuropsychological skills mentioned; the other component of the model is the motor, which relates directly to the previous component and is mediated by the four EFs that control behavior.

Accordingly, Nigg (2001) shows clear evidence of the existence of a deficit in ADHD of different forms of executive inhibitory responses, but raises some doubts and questions about whether ADHD would be caused by a primary or secondary inhibitory disorder. To Nigg, although studies are consistent in the presence of an impulsive ADHD and disturbed behavior, the concept of inhibition should be refined, distinguishing between dependent inhibition of executive control and dependent inhibition of motivational Control; in turn, it suggests that the association between domains and deficits in ADHD is more related to inhibition on the strength of a major boost.

Attention deficit hyperactivity disorder is indeed associated with poor cognitive control, particularly inhibitory control (Willcutt et al., 2005; Chamberlain et al., 2011), this could explain

why people with ADHD have slower RTs, suggesting the use of more time to inhibit prepotent responses in this population (Shen et al., 2011).

The inhibitory deficit in ADHD is associated with both structural and functional abnormalities in the frontostriatal and frontoparietal circuits, often revealing hypoactivation in prefrontal type tasks for go/no go, compared to the typical population (De La Fuente et al., 2013; Hart et al., 2013). Hervey et al. (2006) and Tamm et al. (2012) suggest that ADHD symptoms include poor performance on neuropsychological measures of inhibition, as well as associated measures (lack of foresight, lack of insight, difficulty delaying gratification, poor organization, poor sense of time, excessive responses).

Various studies of children with ADHD have identified alterations in sustained attention and inhibitory control, which leads to poor self-regulation and behavioral difficulties (Puentes-Rozo et al., 2008). These findings support the theory of the involvement of multioperational location systems in ADHD, including prefrontal and posterior cortical, reticular thalamic, striatal, limbic and mediated connections by specific neurotransmitter systems (Barkley, 2006).

Based on the above, the lack of inhibitory control in ADHD should not only be related to behavioral and cognitive impairments, but also to emotional disturbances, and although the deficit in emotional regulation is not currently one of the symptoms of ADHD diagnoses, various theoretical proposals suggest that it is a fundamental aspect of the disorder (Barkley, 2006).

Individuals with ADHD often have symptoms such as irritability, moodiness, low tolerance to frustration, and sudden and unpredictable changes associated with negative emotions such as anger and sadness (Sobanski et al., 2010), which could be explained by a deficit in emotional regulation, due to alterations in inhibitory control, as demonstrated by several studies which documented that individuals with ADHD not only suffer from attention difficulties, disorganization, hyperactivity and impulsivity, but also various emotional problems, such as emotional liability, excessive emotional reactivity, and irritability (Sobanski et al., 2010; Schoemaker et al., 2012; Arnett et al., 2013).

To Barkley (2006), emotional self-regulation is defined as a set of business processes that enable modular emotions and, upon receipt of a dysfunction, can lead to increased emotional responses to certain situations, as well as less empathy and less ability to regulate emotional states, hence the difficulties that individuals with ADHD have expressing emotions, a result of a primary dysfunction in the inhibitory control processes.

POST-TRAUMATIC STRESS DISORDER

Conceptualization, Prevalence, Comorbidity, and Clinical Criteria

According to the APA and the guidance provided in the DSM-5 (American Psychiatric Association [APA], 2013), PTSD is characterized as a psychiatric disorder, described as a categorical entity clinical order. It is currently classified as one of the disorders related to trauma and stress factors, and can occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, an act of terrorism, war or combat, violent personal assault or rape. PTSD is part of a real disorder that leads to short and long term involvement after having experienced or witnessed an event of great emotional impact (Bryant et al., 2011; Sard, 2011). Psychological distress following exposure to a traumatic or stressful events is variable. It has been shown that some people who have been exposed to a stressful or traumatic event do not exhibit clinical features related to PTSD or pathogenesis. This reveals a major contribution by modern science in relation to the existing biological predisposition in some individuals associated with a low susceptibility to this disorder, and therefore provides arguments that PTSD represents a specific phenotype associated with a failure to recover from the normal effects of trauma (Yehuda and LeDoux, 2007).

Regarding the prevalence of PTSD, the data tends to vary according to the diagnostic criteria used to define the disorder, the evaluation procedures implemented, the characteristics of the sample and the context in which the event occurred. All these factors must be considered when studying the phenomenon (Doctor et al., 2011). In the USA, the lifetime risk for PTSD, using the DSM-IV (American Psychiatric Association [APA], 1994) criteria, at the age of 75 years was 8.7% (American Psychiatric Association [APA], 2013). The annual prevalence among USA adults is about 3.5% (Kessler and Wang, 2008). The estimates reported in Europe and most of Asia, Africa and Latin America are lower, at a volume of 0.5–1.0% (Kessler et al., 2005). Although, different groups show different levels of exposure to traumatic events, the conditional probability for PTSD may also vary between different cultural groups when they develop a similar level of exposure. The PTSD rates are higher among veterans and other people whose profession presents a high risk of traumatic exposure (e.g., police, firefighters, emergency medical personnel). The highest rates (ranging from a third to more than half of those exposed) are among the survivors of rape, military combat, captivity and confinement and political or ethnic genocide (Chapman and Diaz-Arrastia, 2014). Classic reference studies have shown that traumatic events with a greater probability of causing a disorder for both men and women are: rape, war, aggression or witness of a murder, and suffering physical abuse in the early stages of life (Kessler et al., 2005; Ogle et al., 2013).

Individuals with PTSD are 80% more likely to have symptoms that meet diagnostic criteria for at least one other mental disorder (e.g., depression, bipolar disorder, anxiety or substance abuse disorders; de Jong et al., 2001; American Psychiatric Association [APA], 2013). Studies with military personnel and veterans reveal a joint incidence of PTSD and mild traumatic brain injury for almost 48% of cases (Chapman and Diaz-Arrastia, 2014). Similarly, there is considerable comorbidity between PTSD and a major neurocognitive disorder (Doctor et al., 2011; Maksimovskiy et al., 2014; Pagotto et al., 2015), including a high association between PTSD and a significant decline in physical and mental health (Blakeley and Jansen, 2013; Pacella et al., 2013). The essential feature for the start of a PTSD diagnosis is the appearance of symptoms after

exposure to one or more traumatic events, either directly or indirectly experienced, such as witnessing something experienced by others. According to the DSM-5 (American Psychiatric Association [APA], 2013) criteria are applicable for adults, adolescents and children over 6 years of age, such as the presence of symptoms persisting for more than a month after experiencing the stressor event. The alteration leads to clinically significant distress or impairment in social, occupational or other important areas of functioning of the individual. The alteration cannot be attributed to the physiological effects of a substance (e.g., drugs, alcohol) or another medical condition (American Psychiatric Association [APA], 2013; Friedman, 2013).

Symptoms that form as a result of the traumatic experience are organized into categories: *Re-experiences or intrusions, Avoidance, Persistent negative alterations in ognition and mood,* and *Increased excitability* (Bryant et al., 2011; American Psychiatric Association [APA], 2013). Currently, there are criteria for children under 6 years in relation to the diagnosis of PTSD, as well as indications of clinical order as to the late expression of the disorder (Friedman et al., 2011; American Psychiatric Association [APA], 2013). Psychiatric indications are clear as to their non-linearity in the symptomatic expression in PTSD, as their presentation is varied, occurring specifically in many cases and in others displaying a combination of symptoms (Friedman, 2013). According to the literature, during the development and course of PTSD the symptoms usually begin within the first 3 months after the trauma, although there may be a delay of months, or even years, before the diagnostic criteria are met, which has been called "delayed expression" disorder (Greenberg et al., 2015). It must also specify if the individual experiences persistent dissociative symptoms (Friedman et al., 2011; American Psychiatric Association [APA], 2013). See **Table 2**.

Biological Bases in Post-traumatic Stress Disorder

Irregularities in the biological system involved in the response to stressful events largely lead to damages in the body, setting a pathological mechanism, compared to normal behavior (Yehuda and LeDoux, 2007; Skelton et al., 2012). Dysfunctions in the spinal sympathetic-adrenal-axis and the hypothalamic-pituitary-adrenal-cortical axis, neuroendocrine dysregulation in glutamatergic, noradrenergic, and serotonin systems result in an imbalance and consequently an increased vulnerability to developing PTSD (Pitman et al., 2012).

Studies using models of psychological stress to evaluate the function of the HPA axis revealed an exaggerated cortisol response and hypersecretion of CRH in the PTSD-state, as a result of physiological failures of the system (Dedovic et al., 2009; Sherin and Nemeroff, 2011; Pitman et al., 2012). Paradoxically, there is evidence showing low plasma cortisol levels and an increase in the negative feedback of the HPA axis under basal conditions (Pitman et al., 2012). The presence of low concentrations of cortisol in people who survive traumatic events is a fact that seems contrary to the idea that stress may be associated with elevated levels of cortisol. One explanation that can be made is that in the course of adaptation to trauma, low cortisol concentrations are detected first, reflecting a chronic adaptation of the HPA axis to stress.

Increased and persistent activation of CRH has also been associated with increased activity of the autonomic nervous system in PTSD victims, particularly in a group of women with a history of sexual abuse in childhood with symptoms of depression and anxiety (Heim et al., 2000). The increase in the negative feedback generated by the cortisol could offer an explanation to why the concentration of cortisol is low in the presence of elevated levels of CRH. Yehuda and LeDoux (2007) propose that chronic release of CRH produces an abnormal response by the pituitary gland. Since the number and sensitivity of lymphocytic glucocorticoid receptors is increased, the negative feedback is also increased, causing an attenuation of the cortisol. This increased negative feedback contrasts with the drop that occurs in depression, in which the chronic release of CRH causes decreased negative feedback leading to hypercortisolism and down-regulation of glucocorticoid receptors (Sherin and Nemeroff, 2011; Pitman et al., 2012). See **Figure 4**.

The hypothesis, which postulates that it exists because of chronic stress on the system, is based on the principle known as down-regulation of the GABAergic system, which leads to an excessive and constant activation of glutamate, which can induce long-term synaptic changes and therefore can damage the cognitive and emotional order. Equally important is the inhibition of GABAergic anomalies associated with cellular toxicity, which leads to high concentrations of harmful cell agents, and therefore a decrease in neuroplasticity, and in extreme cases, their death (Hasler et al., 2010; Sherin and Nemeroff, 2011; Pitman et al., 2012). Biochemical studies also reported a central noradrenergic dysfunction, associated with psychiatric symptoms of PTSD, indicating, in some cases, a noradrenergic hypersensitivity and a possible down-regulation of neural receptors that affect metabolic activity (Sherin and Nemeroff, 2011; Pitman et al., 2012; Yamamoto et al., 2013). The regulation of serotonin (5-HT) and consequently the release of corticosteroids under stressful events are positively associated with increased secretion of CRH and PTSD (Sherin and Nemeroff, 2011).

Neural Circuitry Alterations after Traumatic Events

Changes of the biological order, in most cases, lead to structural and functional flaws in several neural circuits after traumatic events (Bremner et al., 2008). The repercussions are evident in the set of clinical symptoms of the disorder (Suvak and Barrett, 2011). Affectations of anatomical and functional natures have been identified in the neurocircuits, especially in the medial PFC, hippocampus, and amygdala (Shin et al., 2006; Herringa et al., 2012). Similarly, cortical regions such as the insular cortex, anterior cingulate cortex, thalamus, and subcortical limbic structures have become important in understanding the anomalies present in PTSD (Herringa et al., 2012). Although, there is a high reproducibility in terms of deficits in classical structures of the human nervous system, there are also novel

TABLE 2 | Summary of specific criteria and symptoms for the diagnosis of PTSD (American Psychiatric Association [APA], 2013).

Re-experiences or intrusions (1/5)	
(1) Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).	(2) Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).
(3) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring.	(4) Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
(5) Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).	
Avoidance (1/2)	
(1) Avoidance or efforts to avoid distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).	(2) Avoidance or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
Persistent negative alterations in cognition and mood (2/7)	
(1) Inability to remember an important aspect of the traumatic event(s).	(2) Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world.
(3) Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.	(4) Persistent negative emotional state.
(5) Markedly diminished interest or participation in significant activities.	(6) Feelings of detachment or estrangement from others.
(7) Persistent inability to experience positive emotions.	
Increased excitability (2/6)	
(1) Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.	(2) Reckless or self-destructive behavior.
(3) Hypervigilance.	(4) Exaggerated startle response.
(5) Problems with concentration.	(6) Sleep disturbance.

Applies to adults, adolescents and children over 6 years. The essential feature (PTSD) is the development of symptoms after exposure to one or more traumatic events. The duration of symptoms of disturbance should be more than 1 month. Dissociative symptoms should not be attributed to the physiological effects of a substance. (/): symptoms required for the category. The disturbance causes clinically significant distress or impairment in important social, occupational, or other areas of functioning.

reports in the scientific literature that reveal the complexity of the neurobiological mechanisms involved in the expression and development of psychopathology in PTSD (Herringa et al., 2012; Patel et al., 2012). There is no equality regarding variables such as study design, type of target population, biological technique, time of occurrence of the disorder, the expression of symptoms and its comorbidities with others, leading to absolute certainty of one single structure and a single key fault disorder (Etkin and Wager, 2007; Pitman et al., 2012).

The volume reduction in the hippocampus and hippocampal atrophy phenomenon detected in patients with chronic PTSD has been widely reported (Shin et al., 2006; Pitman et al., 2012). The most widespread hypothesis corresponds to a phenomenon of cytotoxicity and cell death, resulting from excessive stimulation of the system (Pitman et al., 2012). A decrease in hippocampal activation during symptomatic expression has also been reported, as well as in performing memory tasks involving a judgment of emotional valences (Sherin and Nemeroff, 2011). Conversely, changes in the system (5-HT) reach defined alterations in hippocampal increased activity and severity of symptoms in PTSD (Bremner, 2006; Bremner et al., 2008; Sherin and Nemeroff, 2011).

Amygdala deficits lead to flaws in the evaluation and regulation of biologically relevant threat signals. There is evidence of abnormalities in the functionality of the amygdala in PTSD, and increased startle response has been postulated to represent an increase in function (Bremner, 2006). Because of this, a large brain circuitry is involved in their functional ability, which is consequently committed to the ventromedial PFC and rostral anterior cingulate region (Sherin and Nemeroff, 2011; Pitman et al., 2012). Similarly, chronic PTSD has been correlated with a reduction in the dorsolateral prefrontal parietal gray matter and cingulate cortex (Pitman et al., 2012). The duration of the disorder has been analyzed as a direct proportion to the reduction in gray matter and the severity of the symptoms (Eckart et al., 2011; Chen et al., 2012; Pitman et al., 2012). Effects on the brain's medial diencephalic region, specifically the thalamus, by glutamatergic system failures have been associated with an expression of dissociative states in PTSD (Bremner et al., 2008). It is speculated that such dissociation occurs as a result of alterations in the thalamic transmission, which can be due either to a decrease in entries in the thalamus, which generates a suppression of emotional memories, or charging excessive noradrenergic input stimuli in the thalamus (O'Brien and Nutt, 1998).

Sartory et al. (2013) recently demonstrated a greater number of interconnected cortical areas involved in shaping the symptoms, specifically re-experiencing on a recurring basis. PTSD patients showed significant activation in the mid-line

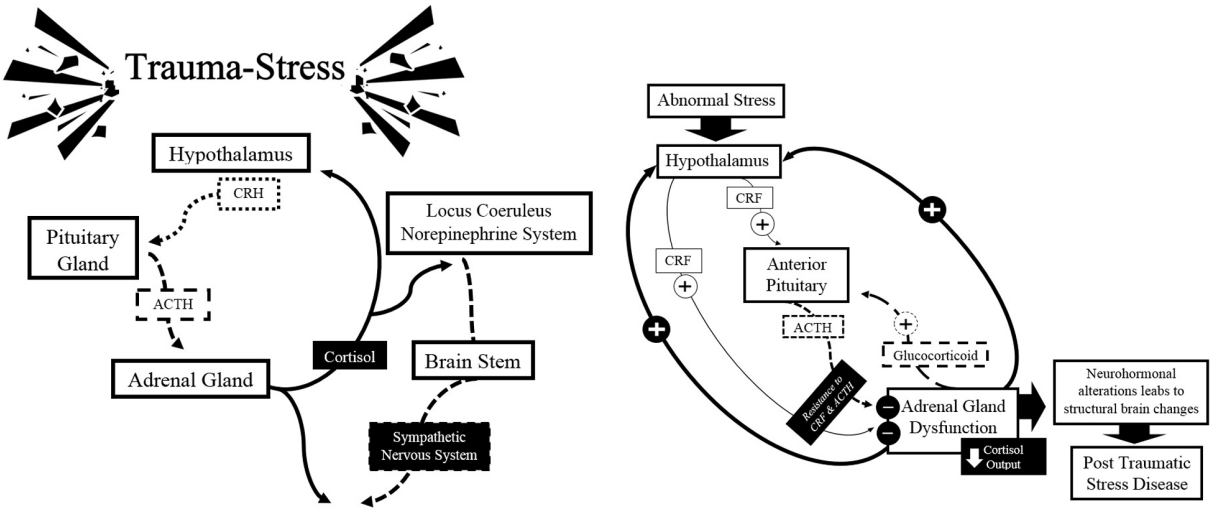

FIGURE 4 | Schematic summary of the classical model of neurobiology in the expression of PTSD: hypothalamic-pituitary-adrenal axis. Source: made by myself.

retrosplenial cortex and precuneus region in response to stimuli associated with the trauma. Likewise, a hyperarousal of the anterior cingulate gyrus was also evident as well as the bilateral amygdala and hypoactivation in sensory association areas, which could indicate that the attentional system required to meet the demand of a task is compromised by centralization of a traumatic memory, generating an associative learning bias due to its intrusive and disturbing connotations.

It is important to note that although research reveals a variety of structural and functional changes by neuroimaging evidence due to exposure to a traumatic event, these changes have been associated with the trauma and therefore care should be taken not to consider them as a cause-effect (Sherin and Nemeroff, 2011; Patel et al., 2012).

Genetic vulnerability, as well as the pre-existence of different abnormalities, are aspects that could be acting as a development risk factor of a symptomatic trauma or neurodegenerative pattern after the trauma (Miller and Sadeh, 2014). Knowledge of the genetic basis and neural pathways involved in the etiology and maintenance of the disorder allow better understanding from a clinical perspective (Suvak and Barrett, 2011; Pitman et al., 2012; Skelton et al., 2012).

Post-traumatic Stress Disorder and Inhibitory Control Dysfunction

According to the DSM-5 (American Psychiatric Association [APA], 2013), recurring memories of the event, avoidance of stimuli associated with the traumatic experience, diminished interest in significant activities, a constant state of hypervigilance, and attentional problems in terms of maintenance, form a pattern of information processing for the majority of PTSD cases.

The central components refer to neurobiological substrate irregularities involving an increased vulnerability in limbic and prefrontal regions, specifically during mnemonic, attentional, emotional and executive processing (Bonelli and Cummings, 2007; Pitman et al., 2012; Chen and Etkin, 2013).

Irregular functioning of inhibitory control, considering the properties of control and regulation, would lead to a permanent imbalance of the nervous system, as well as recurrent failures that would place the cognitive and emotional stability of the subject at risk (MacDonald et al., 2000; Gifford, 2002). The integrity of all executive capabilities provides benefits in terms of the strategy to direct attention and inhibit irrelevant stimuli, thus tending to best guarantee the achievement of a goal (Snyder et al., 2015). Failures in attentional efficiency of the executive control network, mainly in inhibiting interference and attentional failures, have been linked to a decreased ability to control voluntary actions in PTSD patients (Pacheco-Unguetti et al., 2011; Pechtel and Pizzagalli, 2011), as well as difficulties in developing efficient strategies to cope with potentially anxiety-inducing elements (Polak et al., 2012).

Inhibitory control is essential for the exercise of mental flexibility, control and impulsivity interference, WM, self-regulation of emotion and the capacity for analysis and synthesis of behavior (Aron, 2007; Diamond, 2013). An extensive network of frontostriatal circuits are affected in the inhibitory control of patients who have suffered traumatic experiences (Aupperle et al., 2012b; Pitman et al., 2012). Neuropsychological studies have documented anatomical and functional disorders associated with cognitive deficits in patients with PTSD, compared with controls (Bremner, 2006). Long-term effects have been identified in the memory domain for verbal information (McNally, 2006; Brewin, 2011) and visual memory (Marx et al., 2009), declarative memory (Samuelson, 2011), attention (Samuelson et al., 2006; Aupperle et al., 2012a), sustained attention (Vasterling et al., 2002), emotional processing (Milad et al., 2008), WM (Aupperle et al., 2012a), intelligence (Gilbertson et al., 2006), language and communication (McNally, 2006), learning (Samuelson et al., 2006), and processing

speed (Samuelson et al., 2006). Disturbances in executive functioning are important to the large bias in cognitive activity in general (Pollak et al., 2010; Aupperle et al., 2012b).

Relationship between Attention Deficit Disorder/Hyperactivity and Post-traumatic Stress Disorder

The inhibitory control component of interest in this review lies mainly in its importance as a central aspect of EF (Banich, 2009; Diamond, 2013) and as a key mechanism that contributes significantly to the efficiency of the executive system in general (Aron, 2007; Banich, 2009). It is for this reason that the different components that make up the theory associated with EFs are initially highlighted, with special emphasis on inhibitory control.

The structural and functional abnormalities of both ADHD and PTSD are evident in a large and complex brain circuit that comprises frontal and medial areas, as well as the cingulate cortex and thalamus, the hippocampal formation and the amygdaloid complex (Bonelli and Cummings, 2007; Pitman et al., 2012; Etkin et al., 2013). This creates a permanent interest in their revision, seeking greater clarity of their underlying mechanisms, which can be a possible route in terms of objective biomarkers and its future use in the monitoring of each pathology.

On the other hand, endocrine factors and brain circuits are involved in the optimal functioning of inhibitory control, especially in the dorsal and ventral PFC, the supplementary motor area, anterior cingulate and parietal and occipital lobe. Such irregularities in the neural mechanisms are associated with the severity of the symptoms in both ADHD and PTSD, referring globally to deficits in attentional systems (Gifford, 2002; Rae et al., 2015).

Regarding the link between these two diagnostic entities, there is evidence suggesting comorbidity with prevalence estimates ranging from 12 to 37% (Adler et al., 2004). The comorbidity described is associated with problems in emotional modulation (arousal levels) that are common to both disorders (hyperarousal and hypoactivation; Harrington et al., 2012).

Adler et al. (2004) suggest that ADHD can become a risk factor that increases vulnerability to developing PTSD after exposure to a traumatic event, based on the finding that the patients with PTSD that they evaluated reported higher levels of ADHD in childhood compared to patients with other disorders.

A study by Koenen et al. (2007) showed patients were 50% more likely to experience psychological trauma if there was a history associated with hyperactivity problems, antisocial behavior, and irritability during childhood, compared to individuals with no such history.

Authors such as Adams (2010) have argued that experiencing traumatic events in childhood is strongly associated with development of psychiatric conditions for life, such as personality disorders, behavioral disorders, ADHD, depression, anxiety, substance abuse and PTSD; as well as developmental delay, impaired cognitive skills, learning difficulties, and even a lower IQ.

In 2000, Ford and collaborators revealed results that suggest that the presence of ADHD and Oppositional Defiant Disorder is more common in patients with a history of physical or sexual abuse, pointing to abuse as a significant risk factor for development of behavioral disorders.

Thus, ADHD during childhood increases exposure to trauma, including physical injuries, physical and sexual abuse, neglect, among others (Koenen et al., 2007; Ouyang et al., 2008). In addition, children who are exposed to traumatic events may be more vulnerable to experiencing an exacerbation of the symptoms of ADHD, such as those related to the regulation of impulses and physiological hyperarousal (Ford et al., 2000; Harrington et al., 2012).

The symptoms that reflect the overlap between ADHD and PTSD include irritability, excessive motor activity, learning disabilities, attention, the attentional shift and concentration difficulties, impulsive behavior, and exaggerated startle responses (Hervey et al., 2004; Daud and Rydelius, 2009), clearly demonstrating symptoms common to both disorders associated with EFs. Thus, alterations in the EFs due to ADHD may explain the high reporting of the disorder as a risk factor for developing PTSD, as suggested by several studies (Nigg et al., 2002; Martel and Nigg, 2006; Volkow et al., 2011).

Generally, according to Bernardi et al. (2012), high rates of impulsive behavior, inattentiveness, and alterations in inhibitory control in individuals with ADHD could provide explanations for the increased risk of trauma.

According to a study by Harrington et al. (2012), which used a confirmatory factor analysis to establish the level of correlation between ADHD and PTSD, the "lack of attention" in ADHD was identified as a factor associated moderately with symptoms of avoidance in the PTSD. Based on this result, the study authors explain that inattention in ADHD and avoidance symptoms in PTSD may reflect similar changes in cognitive control mechanisms, creating problems of distraction and disorganization in ADHD and difficulty in emotionally suppressing intrusive thoughts in PTSD, exposing possible associations between the two disorders related to alterations in inhibitory control.

Swick et al. (2013) evaluated the variability in RT as an indicator of executive dysfunction, specifically as it relates to difficulties in inhibitory control and excessive mental disorder in war veterans and controls, through the go/no go inhibition task, finding that individuals with PTSD had significantly greater variability in RT than the controls, suggesting that they are less successful in inhibiting appropriate responses; in addition, other symptoms such as attentional impulsivity are also present in individuals with ADHD. The findings of this study pointed to deficits in cognitive control processes, specifically top–down, which could contribute to the continuation of PTSD symptoms.

Greater RT variability in cognitive tasks has been associated with a greater propensity toward negative affect (Ode et al., 2011), among other conditions, for developmental disorders (Tamm et al., 2012) such as ADHD. In fact, the increased variability in RTs in ADHD is a highly replicable finding (Hervey et al., 2006; Swick et al., 2013; Tarantino et al., 2013). Among the various explanations for this increased RT variability are: deficits

in sustained attention, problems processing time information, and difficulties in regulating behavior (Johnson et al., 2007; Tamm et al., 2012), resulting in a general marker of executive dysfunction (Ode et al., 2011).

However, it is not known whether deficiencies in the general cognitive mechanism such as top–down can account for similar deficits in several disorders, or whether different mechanisms are involved (Swick et al., 2013).

Based on the above, it could be argued that the cognitive, emotional and behavioral disfunctions that characterize both ADHD and PTSD may result from the overlapping of neural substrates.

GENERAL CONCLUSION

As a result of the review of literature associated with ADHD and PTSD, it can be said that these two clinical entities are characterized by a set of signs and symptoms that detail their particular neurobiology, thus allowing a better understanding for clinical management and behavioral aspects to be taken into account in the different diagnoses and future interventions.

Inhibitory control is a cognitive process that plays an important role in ADHD and PTSD; giving rise to the possibility that research generates experimental approaches where inhibitory control is associated with emotional components. In this regard, it would be possible to act on the "psychological distress" that leads these two disorders, especially regarding behavioral disturbances, threatening the adaptation of the affected subject to different contexts in which they operate, including comorbidity with various other mental disorders (Bonelli and Cummings, 2007; Etkin et al., 2013).

Current information on the link between ADHD and PTSD is inconclusive, which still allows for the development of knowledge and interest in its disclosure, primarily through the generation of new research.

On the other hand, continuing to generate associated research will undoubtedly provide a greater understanding as to the specificity of the neurobiological aspects present in both psychiatric conditions. In this sense, the following may be proposed: (1) Biomarker analysis and its future use in the monitoring of each pathology. Genetic and neurophysiological evidence can be integrated into the study of brain hemodynamics using fMRI, PET and SPECT techniques, for example, as well as EEG by monitoring spontaneous and induced electrical activity. Thus, we could better understand the physiological and cognitive mechanisms underlying these pathologic entities, generating new possibilities for clinical and experimental settings. (2) Use of neuropsychological assessment and neuroimaging in order to map the brain. It is vital to develop studies that record biological activity while simultaneously making assessments via cognitive tests (specifically frontal lobe assessment using EF tests). It would be more appropriate to combine traditional and ecological neuropsychological tools in order to obtain more reliable results. (3) Comorbidity and monitoring of the disorder. Given the explanations outlined in this review regarding the increased chance of individuals diagnosed with ADHD suffering from PTSD, is it possible to argue that ADHD worsens the outcome of PTSD, and can we therefore propose a comorbidity? If yes, this could be included in future diagnostic manuals to show the interaction between the two pathologies. Thus, it would contribute not only to the understanding and diagnosis of both diseases, but also to its monitoring at both the clinical and research levels.

Finally, it should be expected that the inclusion of technological tools in the diagnostic and intervention stage will allow better recreation of the scenarios of daily life, thus increasing understanding of rarely addressed cognitive and emotional strategies that are important in shaping ADHD and PTSD.

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LM, EP, CS, MT, CT conceptualized and designed the work. LM, EP, CS drafted the work. LM, EP, CS, MT, CT critically revised and approved the manuscript.

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REFERENCES

Adams, E. J. (2010). *Healing invisible wounds: Why Investing in Traumainformed Care for Children Makes Sense*. Washington, DC: Justice Policy Institute.

Adler, L. A., Kunz, M., Chua, H. C., Rotrosen, J., and Resnick, S. G. (2004). Attentiondeficit/hyperactivity disorder in adult patients with posttraumatic stress disorder (PTSD): Is ADHD a veulnerability factor? *J. Atten. Disord.* 8, 11–16. doi: 10.1177/108705470400800102

American Psychiatric Association [APA] (1994). *DSM-IV. Diagnostic and Statistical Manual of Mental Disorders*, 4th Edn. Washington, DC: Author.

American Psychiatric Association [APA] (2013). *DSM-5. Diagnostic and Statistical Manual of Mental Disorders*, 5th Edn. Washington, DC: Author.

Ardila, A. (2008). On the evolutionary origins of executive functions. *Brain Cogn.* 68, 92–99. doi: 10.1016/j.bandc.2008.03.003

Arnett, A. B., MacDonald, B., and Pennington, B. F. (2013). Cognitive and behavioral indicators of ADHD symptoms prior to school age. *J. Child Psychol. Psychiatry* 54, 1284–1294. doi: 10.1111/jcpp.12104

Arnsten, A. F., and Li, B. M. (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biol. Psychiatry* 57, 1377–1384. doi: 10.1016/j.biopsych.2004.08.019

Arnsten, A. F., Steere, J. C., and Hunt, R. D. (1996). The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention deficit hyperactivity disorder. *Arch. Gen. Psychiatry* 53, 448–455. doi: 10.1001/archpsyc.1996.01830050084013

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *Neuroscientist* 13, 214–228. doi: 10.1177/1073858407299288

Aron, A. R., Robbins, T. W., and Poldrak, R. A. (2004). Inhibition and the right inferior frontal cortex. *Trends Cogn. Sci.* 8, 170–177. doi: 10.1016/j.tics.2004.02.010

Aupperle, R. L., Allard, C. B., Grimes, E. M., Simmons, A. N., Flagan, T., Behrooznia, M., et al. (2012a). Dorsolateral prefrontal cortex activation during emotional anticipation and neuropsychological performance in posttraumatic stress disorder. *Arch. Gen. Psychiatry* 69, 360–371. doi: 10.1001/archgenpsychiatry.2011.1539

Aupperle, R. L., Melrose, A. J., Stein, M. B., and Paulus, M. P. (2012b). Executive function and PTSD: disengaging from trauma. *Neuropharmacology* 62, 686–694. doi: 10.1016/j.neuropharm.2011.02.008

Banich, M. T. (2009). Executive function: the search for an integrated account. *Curr. Dir. Psychol. Sci.* 18, 89–94. doi: 10.1111/j.1467-8721.2009.01615.x

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol. Bull.* 121, 65–94. doi: 10.1037/0033-2909.121.1.65

Barkley, R. A. (2006). "A theory of ADHD," in *Attention-Deficit Hyperactivity Disorder. A Handbook for Diagnosis and Treatment*, ed. R. A. Barkley (New York, NY: Guilford Press), 297–233.

Bernardi, S., Faraone, S. V., Cortese, S., Kerridge, B. T., Pallanti, S., Wang, S., et al. (2012). The lifetime impact of attention-deficit hyperactivity disorder: results from the national epidemiologic survey on alcohol and related conditions. *Psychol. Med.* 42, 875–887. doi: 10.1017/S003329171100153X

Biederman, J., Petty, C. R., Wozniak, J., Wilens, T. E., Fried, R., Doyle, A., et al. (2011). Impact of executive function deficits in youth with bipolar I disorder: a controlled study. *Psychiatry Res.* 186, 58–64. doi: 10.1016/j.psychres.2010.08.029

Blakeley, K., and Jansen, D. J. (2013). *Post-Traumatic Stress Disorder and Other Mental Health Problems in the Military: Oversight Issues for Congress*. Washington, DC: Congressional Research Service.

Bobb, A. J., Addington, A. M., Sidransky, E., Gornick, M. C., Lerch, J. P., Greenstein, D. K., et al. (2005). Support for association between ADHD and two candidate genes: NET1 and DRD1. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 134B, 67–72. doi: 10.1002/ajmg.b.30142

Bonelli, R., and Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues Clin. Neurosci.* 9, 141–151.

Boutros, N., Fraenkel, L., and Feingold, A. (2005). A four-step approach for developing diagnostic tests in psychiatry: EEG in ADHD as a test case. *J. Neuropsychiatry Clin. Neurosci.* 17, 455–464. doi: 10.1176/jnp.17.4.455

Bremner, J. D. (2006). The relationship between cognitive and brain changes in posttraumatic stress disorder. *Ann. N. Y. Acad. Sci.* 1071, 80–86. doi: 10.1196/annals.1364.008

Bremner, J. D., Elzinga, B., Schmahl, C., and Vermetten, E. (2008). Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog. Brain Res.* 167, 171–186. doi: 10.1016/S0079-6123(07)67012-5

Brewin, C. R. (2011). The nature and significance of memory disturbance in posttraumatic stress disorder. *Annu. Rev. Clin. Psychol.* 7, 203–227. doi: 10.1146/annurev-clinpsy-032210-104544

Bruckmann, S., Hauk, D., Roessner, V., Resch, F., Freitag, C. M., Kammer, T., et al. (2012). Cortical inhibition in attention deficit hyperactivity disorder: new insights from the electroencephalographic response to transcranial magnetic stimulation. *Brain* 135, 2215–2230. doi: 10.1093/brain/aws071

Bryant, R. A., Friedman, M. J., Spiegel, D., Ursano, R., and Strain, J. (2011). A review of acute stress disorder in DSM-5. *Depress. Anxiety* 28, 802–817. doi: 10.1002/da.20737

Carlson, S. M., and Wang, T. (2007). Inhibitory control and emotion regulation in preschool children. *Cogn. Dev.* 22, 489–510. doi: 10.1016/j.cogdev.2007.08.002

Castellanos, F. X. (1997). Toward a pathophysiology of attention-deficit/hyperactivity disorder. *Clin. Pediatr.* 36, 381–393. doi: 10.1177/000992289703600702

Chamberlain, S. R., Robbins, T. W., Winder-Rhodes, S., Müller, U., Sahakian, B. J., Blackwell, A. D., et al. (2011). Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol. Psychiatry* 69, 1192–1203. doi: 10.1016/j.biopsych.2010.08.019

Chapman, J. C., and Diaz-Arrastia, R. (2014). Military traumatic brain injury: a review. *Alzheimers Dement.* 10, S97–S104. doi: 10.1016/j.jalz.2014.04.012

Chen, A. C., and Etkin, A. (2013). Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. *Neuropsychopharmacology* 38, 1889–1898. doi: 10.1038/npp.2013.122

Chen, Y., Fu, K., Feng, C., Tang, L., Zhang, J., Huan, Y., et al. (2012). Different regional gray matter loss in recent onset PTSD and non PTSD after a single prolonged trauma exposure. *PLoS ONE* 7:e48298. doi: 10.1371/journal.pone.0048298

Chung, H. J., Weyandt, L. L., and Swentosky, A. (2014). "The Physiology of executive functioning," in *Handbook of Executive Functioning*, eds S. Goldstein and J. A. Naglieri (New York, NY: Springer Science+Business Media), 13–27.

Collette, F., Hogge, M., Salmon, E., and Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience* 139, 209–221. doi: 10.1016/j.neuroscience.2005.05.035

Collette, F., Van der Linden, M., Delfiore, G., Degueldre, C., Luxen, A., and Salmon, E. (2001). The functional anatomy of inhibition processes investigated with the Hayling task. *Neuroimage* 14, 258–267. doi: 10.1006/nimg.2001.0846

Collins, A., and Koechlin, E. (2012). Reasoning, learning, and creativity: frontal lobe function and human decision-making. *PLoS Biol.* 10:e1001293. doi: 10.1371/journal.pbio.1001293

Comings, D. E. (2001). Clinical and molecular genetics of ADHD and Tourette syndrome. Two related polygenic disorders. *Ann. N. Y. Acad. Sci.* 931, 50–83. doi: 10.1111/j.1749-6632.2001.tb05773.x

Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di Martino, A., Milham, M. P., et al. (2012). Towards systems neuroscience of ADHD: a meta-analysis of 55 fMRI studies. *Am. J. Psychiatry* 169, 1–28. doi: 10.1176/appi.ajp.2012.11101521

Daud, A., and Rydelius, P. A. (2009). Comorbidity/overlapping between ADHD and PTSD in relation to IQ among children of traumatized/non-traumatized parents. *J. Atten. Disord.* 13, 188–196. doi: 10.1177/1087054708326271

de Jong, J. T., Komproe, I. H., Van Ommeren M., El Masri, M., Araya, M., Khaled, N., et al. (2001). Lifetime events and posttraumatic stress disorder in 4 postconflict settings. *JAMA* 286, 555–562. doi: 10.1001/jama.286.5.555

De La Fuente, A., Xia, S., Branch, C., and Li, X. (2013). A review of attention-deficit/hyperactivity disorder from the perspective of brain networks. *Front. Hum. Neurosci.* 7:192. doi: 10.3389/fnhum.2013.00192

Dedovic, K., Duchesne, A., Andrews, A., Engert, V., and Pruessner, J. C. (2009). The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage* 47, 864–871. doi: 10.1016/j.neuroimage.2009.05.074

Diamond, A. (2006). "The early development of executive functions," in *Lifespan Cognitive Mechanisms of Change*, eds E. Bialystok and F. Craik (New York, NY: Oxford University Press), 70–95.

Diamond, A. (2013). Executive functions. *Annu. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

Ditye, T., Jacobson, L., Walsh, V., and Lavidor, M. (2012). Modulating behavioral inhibition by tDCS combined with cognitive training. *Exp. Brain Res.* 219, 363–368. doi: 10.1007/s00221-012-3098-4

Doctor, J. N., Zoellner, L. A., and Feeny, N. C. (2011). Predictors of health-related quality-of-life utilities among persons with posttraumatic stress disorder. *Psychiatric Serv.* 62, 272–277. doi: 10.1176/appi.ps.62.3.272

Doyle, A. E. (2006). Executive functions in attention-deficit/hyperactivity disorder. *J. Clin. Psychiatry* 6, 21–26.

Eckart, C., Stoppel, C., Kaufmann, J., Tempelmann, C., Hinrichs, H., Elbert, T., et al. (2011). Structural alterations in lateral prefrontal, parietal and posterior midline regions of men with chronic posttraumatic stress disorder. *J. Psychiatry Neurosci.* 36, 176–186. doi: 10.1503/jpn.100010

Elliott, R. (2003). Executive functions and their disorders. *Br. Med. Bull.* 65, 49–59. doi: 10.1093/bmb/65.1.49

Etkin, A., Gyurak, A., and O'Hara, R. (2013). A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues Clin. Neurosci.* 15, 419–429. doi: 10.1016/j.jad.2005.11.006

Etkin, A., and Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatry* 164, 1476–1488. doi: 10.1176/appi.ajp.2007.07030504

Ford, J. D., Racusin, R., Ellis, C. G., Daviss, W. B., Reiser, J., Fleischer, A., et al. (2000). Child maltreatment, other trauma exposure, and posttraumatic symptomatology among children with oppositional defiant and attention deficit hyperactivity disorders. *Child Maltreat.* 5, 205–217. doi: 10.1177/1077559500005003001

Friedman, M. J. (2013). Finalizing PTSD in DSM-5: getting here from there and where to go next. *J. Trauma Stress* 26, 548–556. doi: 10.1002/jts.21840

Friedman, M. J., Resick, P. A., Bryant, R. A., and Brewin, C. R. (2011). Considering PTSD for DSM-5. *Depress. Anxiety* 28, 750–769. doi: 10.1002/da.20767

Funahashi, S., and Andreau, J. M. (2013). Prefrontal cortex and neural mechanisms of executive function. *J. Physiol. París* 107, 471–482. doi: 10.1016/j.jphysparis.2013.05.001

Fuster, J. M. (2002). Frontal lobe and cognitive development. *J. Neurocytol.* 31, 373–385. doi: 10.1023/A:1024190429920

Fuster, J. M. (2008). *The Prefrontal Cortex*. London: Academic Press.

Gifford, A. (2002). Emotion and self-control. *J. Econ. Behav. Organ.* 49, 113–130. doi: 10.1016/S0167-2681(02)00061-6

Gilbertson, M. W., Paulus, L. A., Williston, S. K., Gurvits, T. V., Lasko, N. B., Pitman, R. K., et al. (2006). Neurocognitive function in monozygotic twins discordant for combat exposure: relationship to posttraumatic stress disorder. *J. Abnorm. Psychol.* 115, 484–495. doi: 10.1037/0021-843X.115.3.484

Greenberg, N., Brooks, S., and Dunn, R. (2015). Latest developments in post-traumatic stress disorder: diagnosis and treatment. *Br. Med. Bull.* 114, 147–155. doi: 10.1093/bmb/ldv014

Harrington, K. M., Miller, M. W., Wolf, E. J., Reardon, A. F., Ryabchenko, K. A., and Ofrat, S. (2012). Attention-deficit/hyperactivity disorder comorbidity in a sample of veterans with posttraumatic stress disorder. *Compr. Psychiatry* 53, 679–690. doi: 10.1016/j.comppsych.2011.12.001

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., and Rubia, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry* 70, 185–198. doi: 10.1001/jamapsychiatry.2013.277

Hasler, G., Van der Veen, J. W., Grillon, C., Drevets, W. C., and Shen, J. (2010). Effect of acute psychological stress on prefrontal GABA concentration determined by proton magnetic resonance spectroscopy. *Am. J. Psychiatry* 167, 1226–1231. doi: 10.1176/appi.ajp.2010.09070994

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., et al. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 284, 592–597. doi: 10.1001/jama.284.5.592

Herringa, R., Phillips, M., Almeida, J., Insana, S., and Germain, A. (2012). Post-traumatic stress symptoms correlate with smaller subgenual cingulate, caudate, and insula volumes in unmedicated combat veterans. *Psychiatry Res.* 203, 139–145. doi: 10.1016/j.pscychresns.2012.02.005

Hervey, A. S., Epstein, J. N., and Curry, J. F. (2004). Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. *Neuropsychology* 18, 485–503. doi: 10.1037/0894-4105

Hervey, A. S., Epstein, J. N., Curry, J. F., Tonev, S., Arnold, L. E., Conners, C. K., et al. (2006). Reaction time distribution analysis of neuropsychological performance in an ADHD sample. *Child Neuropsychol.* 12, 125–140. doi: 10.1080/09297040500499081

Hofmann, W., Schmeichel, B. J., and Baddeley, A. D. (2012). Executive functions and self-regulation. *Trends Cogn. Sci.* 16, 174–180. doi: 10.1016/j.tics.2012.01.006

Johnson, K. A., Kelly, S. P., Bellgrove, M. A., Barry, E., Cox, M., Gill, M., et al. (2007). Response variability in attention deficit hyperactivity disorder: evidence for neuropsychological heterogeneity. *Neuropsychologia* 45, 630–638. doi: 10.1016/j.neuropsychologia.2006.03.034

Jurado, M. B., and Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychol. Rev.* 17, 213–233. doi: 10.1007/s11065-007-9040-z

Kane, M. J., Bleckley, M. K., Conway, A. R., and Engle, R. W. (2001). A controlled-attention view of working memory capacity. *J. Exp. Psychol. Gen.* 130, 169–183. doi: 10.1037/0096-3445.130.2.169

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., and Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatry* 62, 617–627. doi: 10.1001/archpsyc.62.6.617

Kessler, R. C., and Wang, P. S. (2008). The descriptive epidemiology of commonly occurring mental disorders in the United States. *Annu. Rev. Public Health* 29, 115–129. doi: 10.1146/annurev.publhealth.29.020907.090847

Koenen, K. C., Moffitt, T. E., Poulton, R., Martin, J., and Caspi, A. (2007). Early childhood factors associated with the development of post-traumatic stress disorder: results form a longitudinal birth cohort. *Psychol. Med.* 37, 181–192. doi: 10.1017/S0033291706009019

Lange, K. W., Reichl, S., Lange, K. M., Tucha, L., and Tucha, O. (2010). The history of attention deficit hyperactivity disorder. *Atten. Defic. Hyperact. Disord.* 2, 241–255. doi: 10.1007/s12402-010-0045-8

Lundervold, A. J., Adolfsdottir, S., Halleland, H., Halmoy, A., Plessen, K., and Haavik, J. (2011). Attention network test in adults with ADHD—the impact of affective fluctuations. *Behav. Brain Funct.* 7, 27. doi: 10.1186/1744-9081-7-27

Lunt, L., Bramham, J., Morris, R. G., Bullock, P. R., Selway, R. P., Xenitidis, K., et al. (2012). Prefrontal cortex dysfunction and "jumping to conclusions": bias or deficit? *J. Neuropsychol.* 6, 65–78. doi: 10.1111/j.1748-6653.2011.02005.x

MacDonald, A. W., Cohen, J. D., Stenger, V. A., and Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288, 1835–1838. doi: 10.1126/science.288.5472.1835

Maksimovskiy, A. L., McGlinchey, R. E., Fortier, C. B., Salat, D. H., Milberg, W. P., and Oscar-Berman, M. (2014). White matter and cognitive changes in veterans diagnosed with alcoholism and PTSD. *J. Alcohol. Drug Depend.* 2, 144. doi: 10.4172/2329-6488.1000144

Martel, M. M., and Nigg, J. T. (2006). Child ADHD and personality/temperament traits of reactive and effortful control, resiliency, and emotionality. *J. Child Psychol. Psychiatry* 47, 1175–1183. doi: 10.1111/j.1469-7610.2006.01629.x

Marvel, C. L., and Desmond, J. E. (2010). Functional topography of the cerebellum in verbal working memory. *Neuropsychol. Rev.* 20, 271–279. doi: 10.1007/s11065-010-9137-7

Marx, B. P., Doron-Lamarca, S., Proctor, S. P., and Vasterling, J. J. (2009). The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes among Iraq-deployed Army soldiers. *J. Int. Neuropsychol. Soc.* 15, 840–852. doi: 10.1017/S1355617709990488

McLoughlin, G., Palmer, J. A., Rijsdijk, F., and Makeig, S. (2014). Genetic overlap between evoked frontocentral theta-band phase variability, reaction time variability, and attention-deficit/hyperactivity disorder symptoms in a twin study. *Biol. Psychiatry* 75, 238–247. doi: 10.1016/j.biopsych.2013.07.020

McNally, R. J. (2006). Cognitive abnormalities in post-traumatic stress disorder. *Trends Cogn. Sci.* 10, 271–277. doi: 10.1016/j.tics.2006.04.00

Miller, M. W., and Sadeh, N. (2014). Traumatic stress, oxidative stress and posttraumatic stress disorder: neurodegeneration and the accelerated-aging hypothesis. *Mol. Psychiatry* 19, 1156–1162. doi: 10.1038/mp.2014.111

Milad, M. R., Orr, S. P., Lasko, N. B., Chang, Y., Rauch, S. L., and Pitman, R. K. (2008). Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J. Psychiatr. Res.* 42, 515–520. doi: 10.1016/j.jpsychires.2008.01.017

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Närhi, V., Lehto-Salo, P., Ahonen, T., and Marttunen, M. (2010). Neuropsychological subgroups of adolescents with conduct disorder. *Scand. J. Psychol.* 51, 278–284. doi: 10.1111/j.1467-9450.2009.00767.x

Nigg, J. T. (2001). Is ADHD an inhibitory disorder? *Psychol. Bull.* 127, 571–598. doi: 10.1037/0033-2909.127.5.571

Nigg, J. T., John, O. P., Blaskey, L. G., Huang-Pollock, C. L., Willcutt, E. G., Hinshaw, S. P., et al. (2002). Big five dimensions and ADHD symptoms: links between personality traits and clinical symptoms. *J. Pers. Soc. Psychol.* 83, 451–469. doi: 10.1037/0022-3514.83.2.451

O'Brien, M., and Nutt, D. (1998). Loss of consciousness and post-traumatic stress disorder: a clue to aetiology and treatment. *Br. J. Psychiatry* 173, 102–104. doi: 10.1192/bjp.173.2.102

Ode, S., Robinson, M. D., and Hanson, D. M. (2011). Cognitive-emotional dysfunction among noisy minds: predictions from individual differences in reaction time variability. *Cogn. Emot.* 25, 307–327. doi: 10.1080/02699931.2010.494387

Ogle, C. M., Rubin, D. C., Berntsen, D., and Siegler, L. C. (2013). The frequency and impact of exposure to potentially traumatic events over the life course. *Clin. Psychol. Sci.* 1, 426–434. doi: 10.1177/2167702613485076

Ouyang, L., Fang, X., Mercy, J., Perou, R., and Grosse, S. D. (2008). Attention-deficit/hyperactivity disorder symptoms and child maltreatment: a population based study. *J. Pediatr.* 153, 851–856. doi: 10.1016/j.jpeds.2008.06.002

Pacella, M. L., Hruska, B., and Delahanty, D. L. (2013). The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review. *J. Anxiety Disord.* 27, 33–46. doi: 10.1016/j.janxdis.2012.08.004

Pacheco-Unguetti, A. P., Acosta, A., Marqués, E., and Lupiáñez, J. (2011). Alterations of the attentional networks in patients with anxiety disorders. *J. Anxiety Disord.* 25, 888–895. doi: 10.1016/j.janxdis.2011.04.010

Pagotto, L. F., Mendlowicz, M. V., Coutinho, E. S., Figueira, I., Luz, M. P., Araujo, A. X., et al. (2015). The impact of posttraumatic symptoms and comorbid mental disorders on the health-related quality of life in treatment-seeking PTSD patients. *Compr. Psychiatry* 58, 68–73. doi: 10.1016/j.comppsych.2015.01.002

Patel, R., Spreng, R. N., Shin, L. M., and Girard, T. A. (2012). Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci. Biobehav. Rev.* 36, 2130–2142. doi: 10.1016/j.neubiorev.2012.06.003

Pechtel, P., and Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology* 214, 55–70. doi: 10.1007/s00213-010-2009-2

Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., et al. (2012). Biological studies of post-traumatic stress disorder. *Nat. Rev. Neurosci.* 13, 769–787. doi: 10.1038/nrn3339

Polak, A. R., Witteveen, A. B., Reitsma, J. B., and Olff, M. (2012). The role of executive function in posttraumatic stress disorder: a systematic review. *J. Affect. Disord.* 141, 11–21. doi: 10.1016/j.jad.2012.01.001

Pollak, S. D., Nelson, C. A., Schlaak, M. F., Roeber, B. J., Wewerka, S. S., Wiik, K. L., et al. (2010). Neurodevelopmental effects of early deprivation in post-institutionalized children. *Child Dev.* 81, 224–236. doi: 10.1111/j.1467-8624.2009.01391.x

Puentes-Rozo, P. J., Barceló-Martínez, E., and Pineda, D. A. (2008). Behavioural and neuropsychological characteristics of children of both sexes, between 6 and 11 years of age, with attention deficit hyperactivity disorder. *Rev. Neurol.* 47, 175–184.

Rae, C. L., Hughes, L. E., Anderson, M. C., and Rowe, J. B. (2015). The prefrontal cortex achieves inhibitory control by facilitating subcortical motor pathway connectivity. *J. Neurosci.* 35, 786–794. doi: 10.1523/JNEUROSCI.3093-13.2015

Ranby, K. W., Boynton, M. H., Kollins, S. H., McClernon, F. J., Yang, C., and Fuemmeler, B. F. (2012). Understanding the phenotypic structure of adult retrospective ADHD symptoms during childhood in the United States. *J. Clin. Child Adolesc. Psychol.* 41, 261–274. doi: 10.1080/15374416.2012.654465

Samuelson, K. W. (2011). Post-traumatic stress disorder and declarative memory functioning: a review. *Dialogues Clin. Neurosci.* 13, 346–351.

Samuelson, K. W., Metzler, T. J., Rothlind, J., Choucroun, G., Neylan, T. C., Lenoci, M., et al. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology* 20, 716–726. doi: 10.1037/0894-4105.20.6.716

Sard, V. (2011). Developmental trauma, complex PTSD, and the current proposal of DSM-5. *Eur. J. Psychotraumatol.* 2, 5622. doi: 10.3402/ejpt.v2i0.5622

Sartory, G., Cwik, J., Knuppertz, H., Schürholt, B., Lebens, M., Seitz, R. J., et al. (2013). In search of the trauma memory: a meta-analysis of functional neuroimaging studies of symptom provocation in posttraumatic stress disorder (PTSD). *PLoS ONE* 8:e58150. doi: 10.1371/journal.pone.0058150

Schoemaker, K., Bunte, T., Wiebe, S. A., Andrews, K., Deković, M., and Matthys, W. (2012). Executive function deficits in preschool children with ADHD and DBD. *J. Child Psychol. Psychiatry* 53, 111–119. doi: 10.1111/j.1469-7610.2011.02468.x

Shen, H. I., Tsai, S. Y., and Duann, J. R. (2011). Inhibition control and error processing in children with attention deficit/hyperactivity disorder: an event-related potentials study. *Int. J. Psychophysiol.* 81, 1–11. doi: 10.1016/j.ijpsycho.2011.03.015

Sherin, J. E., and Nemeroff, C. B. (2011). Post-traumatic stress disorder: the neurobiological impact of psychological trauma. *Dialogues Clin. Neurosci.* 13, 263–278.

Shin, L. M., Rauch, S. L., and Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann. N. Y. Acad. Sci.* 1071, 67–79. doi: 10.1196/annals.1364.007

Singhal, A., Shafer, A. T., Russell, M., Gibson, B., Wang, L., Vohra, S., et al. (2012). Electrophysiological correlates of fearful and sad distraction on target processing in adolescents with attention deficit-hyperactivity symptoms and affective disorders. *Front. Integr. Neurosci.* 6:119. doi: 10.3389/fnint.2012.00119

Skelton, K., Ressler, K. J., Norrholm, S. D., Jovanovic, T., and Bradley-Davino, B. (2012). PTSD and gene variants: new pathways and new thinking. *Neuropharmacology* 62, 628–637. doi: 10.1016/j.neuropharm.2011.02.013

Snyder, H. R., Miyake, A., and Hankin, B. L. (2015). Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Front. Psychol.* 6:328. doi: 10.3389/fpsyg.2015.00328

Sobanski, E., Banaschewski, T., Asherson, P., Buitelaar, J., Chen, W., Franke, B., et al. (2010). Emotional lability in children and adolescents with attention deficit/hyperactivity disorder (ADHD): clinical correlates and familial prevalence. *J. Child Psychol. Psychiatry* 51, 915–923. doi: 10.1111/j.1469-7610.2010.02217.x

Suvak, M. K., and Barrett, L. F. (2011). Considering PTSD from the perspective of brain processes: a psychological construction approach. *J. Trauma Stress* 24, 3–24. doi: 10.1002/jts.20618

Swick, D., Honzel, N., Larsen, J., and Ashley, V. (2013). Increased response variability as a marker of executive dysfunction in veterans with post-traumatic stress disorder. *Neuropsychologia* 51, 3033–3040. doi: 10.1016/j.neuropsychologia.2013.10.008

Tamm, L., Narad, M. E., Antonini, T. N., O'Brien, K. M., Hawk, L. W., and Epstein, J. N. (2012). Reaction time variability in ADHD: A Review. *Neurotherapeutics* 9, 500–508. doi: 10.1007/s13311-012-0138-5

Tarantino, V., Cutini, S., Mogentale, C., and Bisiacchi, P. S. (2013). Time-on-task in children with ADHD: an ex-Gaussian analysis. *J. Int. Neuropsychol. Soc.* 19, 820–828. doi: 10.1017/S1355617713000623

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A. N., and Sutker, P. B. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology* 16, 5–14. doi: 10.1037/0894-4105.16.1.5

Volkow, N. D., Wang, G.-J., Newcorn, J. H., Kollins, S. H., Wigal, T. L., Telang, F., et al. (2011). Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Mol. Psychiatry* 16, 1147–1154. doi: 10.1038/mp.2010.97

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., and Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol. Psychiatry* 57, 1336–1346. doi: 10.1016/j.biopsych.2005.02.006

Yamamoto, K., Shinba, T., and Yoshii, M. (2013). Psychiatric symptoms of noradrenergic dysfunction: a pathophysiological view. *Psychiatry Clin. Neurosci.* 68, 1–20. doi: 10.1111/pcn.12126

Yehuda, R., and LeDoux, L. (2007). Response variation following trauma: a translational neuroscience approach to understanding PTSD. *Neuron* 56, 19–32. doi: 10.1016/j.neuron.2007.09.006

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Executive Functions in Children Who Experience Bullying Situations

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Bullying is characterized by intentional, repetitive, and persistent aggressive behavior that causes damage to the victim. Many studies investigate the social and emotional aspects related to bullying, but few assess the cognitive aspects it involves. Studies with aggressive individuals indicate impairment in executive functioning and decision-making. The objective of this study was to assess hot and cold executive functions in children who experience bullying. A total of 60 children between 10 and 11 years of age were included in the study. They were divided into four groups: aggressors (bullies), victims, bully-victims, and control. Tests for decision-making, inhibitory control, working memory, and cognitive flexibility were used. The bully group made more unfavorable choices on the Iowa Gambling Task, which may indicate difficulties in the decision-making process. The victim group took longer to complete the Trail Making Test (Part B) than aggressors, suggesting lower cognitive flexibility in victims. The hypothesis that aggressors would have lower performance in other executive functions such as inhibitory control, working memory, and cognitive flexibility has not been confirmed. This study indicates that bullies have an impairment of hot executive functions whereas victims have a comparatively lower performance in cold executive functions. In addition to social and cultural variables, neurocognitive and emotional factors seem to influence the behavior of children in bullying situations.

Keywords: bullying, decision-making, executive function, aggressive behavior, cognitive flexibility

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INTRODUCTION

The word bullying is used to characterize intentional repetitive and persistent aggressive behavior toward a victim (Olweus, 1994). There is an uneven power relationship between the aggressor and the victim in bullying due to differences in age, physique, or strength. This difference sustains the behavior of the bully even despite clear signs of discomfort and displeasure on the part of those suffering from it (Smith, 2002).

Bullying aggression can occur by direct physical contact (kicking, punching, pushing, theft, or damage to the victim's objects), psychological aggression (verbal abuse involving nicknames, insults, or mean comments about race, sexuality, religion, and physical features) or indirectly (excluding the victim from playing or group conversations) (Bullock, 2002).

In a bullying situation, children can take on different roles. Aggressing children (bullies) have the intention of causing harm or excluding others (Berger, 2007). Children that are victims suffer from

the constant aggression and often fail to react or get others to stop. Children considered victims-aggressors are those that bully/offend but also suffer aggression, and they differ from aggressors because they are not as popular and usually replicate the aggression with a more fragile child (Bandeira and Hutz, 2012). Bystanders are those children who are not directly involved in the aggression but those who witness bullying. Bystander often do not know how to behave in the face of aggression and become silent for fear of becoming victims, or for not trusting the actions taken by school professionals (Lopes Neto, 2005; Miranda, 2011).

The prevalence of bullying seems to vary depending on the sociocultural context. For example, Berger (2007) reviewed the prevalence of bullying in different countries and found a range between 3 and 27% of bullies and between 9 and 32% of victims. However, methodological differences and the definition of bullying itself make it difficult to establish epidemiological comparisons. Understanding the psychological processes involved in the onset and maintenance of a bullying relationship involves clarifying the cognitive and personality factors of bullies and victims. Koh and Wong (2015) argue that the psychological traits of the aggressors reflect potential adaptive advantages related to sexual selection. However, there is evidence that cognitive deficits and certain personality traits are most frequently found in children and adolescents who bully (Medeiros et al., 2014).

Children who are bullies and bully-victims show more frequent antisocial behavior and lower levels of empathy compared to victims and children who do not experience bullying (Camodeca and Goossens, 2005; Gery et al., 2009; Viding et al., 2011). They also have lower academic performance, an increased school drop-out rate, and higher involvement with the justice system (Gini, 2006). Coolidge et al. (2004) observe that bullying behavior is associated with deficits in executive functioning, conduct disorders, oppositional-defiant disorder, attention deficit hyperactivity disorders (ADHDs), and increased use of substances such as alcohol and marijuana.

Regarding executive functions, Diamond (2013) believes that these functions involve three main centers: inhibitory control, working memory, and cognitive flexibility. According to the author, the other functions such as reasoning, planning and organization are built from these three functions.

Currently, some authors have distinguished executive functions into cold and hot. Cool executive functions are related to cognitive/rational high-order process and are used to general cognitive control. Hot executive functions, in turn, are cognitive/emotional processes related to affective decision making, motivation, and social cognition. According to Damásio (1996), decision-making processes are related to the interpretation of body states and emotional bias defined as somatic markers. The process of somatic markers interpretation is important both to risk perception and decision considering immediate and future outcomes. Antisocial behavior has been associated to impairment in somatic marker processing (Damásio et al., 1996; Séguin, 2004; Sinclair and Gansler, 2006; Tung and Chhabra, 2011). Despites the knowledge of social rules, antisocial subjects present rule-breaking behaviors due to the lack of interpretation of these emotional-somatic signals.

Verlinden et al. (2014) found that children who are not involved in bullying situations as bullies or victims have better scores on intelligence tests. Bullies, victims, and bully-victims have greater difficulty with inhibitory control according to the reports of their parents in the BRIEF Scale. This result suggests a probable deficit in executive functioning related to involvement in bullying situations. Such results, however, have certain limitations. Verlinden et al. (2014) use indirect measures of executive functioning in questionnaires that assess parents' perceptions of such cognitive processes.

Cognitive-emotional aspects of executive functions are poorly investigated in studies on bullying, however, they are particularly important in regulating behavior in social situations (Smith and Jones, 2012). Affective decision-making seems to be related to the presence of various psychopathological conditions such as ADHD; autism spectrum disorders, substance abuse such as alcohol and/or cigarettes; conduct disorders; schizophrenia, as well as behavioral problems such as high disinhibition, self-harm, and aggressive behavior (Best et al., 2002; Ernst et al., 2003, 2010; Verdejo-García et al., 2006; Suhr and Tsanadis, 2007; DeVito et al., 2008; Fairchild et al., 2009; Herrera, 2011; Mata et al., 2011; Sallum et al., 2013). Bullies often have alterations in behavior, therefore, the possibility that decision-making may also be impaired in these individuals cannot be ruled out.

In view of the likely involvement of executive functioning in different behavioral patterns related to bullying, the objective of this study was to evaluate the different components of these functions in groups of bullies, victims, bully-victims, and a control group.

As a hypothesis, we consider that bullies, victims and bully-victims child groups would achieve lower scores on the evaluation of executive functions than the group that has no direct involvement with bullying. Another hypothesis was that the group of aggressors and victims-aggressors would demonstrate lower performance on inhibitory control and decision-making in comparison to victims and controls.

MATERIALS AND METHODS

Sample

Initially, the Peer Aggression and Victimization Scale (PAVS) was applied to 225 students of the 6th grade of two public schools and a private school. After the exclusion of children who did not fit in the pre-established age group, the scales and the free informed consent form were delivered to parents. Children were recruited according to the results of the PAVS scale. Children were excluded if they were 12 years or older (as they would be at a different phase of development, in this case in adolescence), with complaints of uncorrected visual or hearing difficulties and/or those with compromising cognitive impairment. Thirty-nine children completed the individual steps, however, they were not included in data analysis because their parents did not deliver the Strengths and Difficulties Questionnaire.

The sample comprised 60 children (32 females and 28 males), with age between 10 to 11 years and attending sixth grade in middle school. A total of 34 children attended private schools and 26 attended public schools in João Pessoa.

Instruments

Strengths and Difficulties Questionnaire – SDQ (Goodman, 1997)

The instrument used to characterize the sample was the Strengths and Difficulties Questionnaire- SDQ, developed by Goodman (1997) and validated for the Brazilian context by Fleitlich et al. (2000). It is a screening questionnaire that aims to assess mental health of children and adolescents (4–16 years). It has 25 items, divided into five subscales: emotional symptoms, conduct problems, hyperactivity, relationship problems with peers and prosocial behavior. A total index of difficulty which is the sum of the subscales (except sociability) is also generated. The instrument can be used in three versions (self-reporting, a version for parents and a version for teachers). In the present study, we used the version for parents. Each item has three alternatives, false (zero), more or less true (one point) and true (two points).

Bullying Evaluation: Peer Aggression and Victimization Scale (PAVS; Cunha et al., 2009)

The PAVS is a self-reported, 18-item scale, applicable to students attending the second half of elementary school (in general, children from 10 to 15 years of age), that investigates behaviors of bullying and victimization among peers. The child selects the frequency (never, rarely, sometimes, very often, or always) with which they performed or suffered a certain behavior at school during the previous 6 months. The answers were added separately according to the following classification: direct aggression, relational aggression, indirect physical aggression, and victimization. This study did not investigate "indirect physical aggression." From the sum of the scores in each class, participants were divided into subgroups according to the cutoff points (Cunha et al., 2009). The scale was used to classify participants into groups of bullies, victims, and bully-victims, in addition to a control group, by using the following criteria:

(a) Bully group – This group comprises children with a high frequency of behavior in the direct aggression items (score $\geq$ 9) and low (score $\leq$ 12) or moderate (score $\leq$ 16) behavior in the victimization items. Children with high scores only in the relational aggression items were not included.
(b) Victim group – This group comprises children with a high frequency of victimization behavior (score $\geq$ 16) and a low level of direct physical aggression (score $\leq$ 7) and relational aggression (score $\leq$ 6).
(c) Bully-victim group – This group comprises children with a high frequency of direct aggressive behavior (score $\geq$ 9) and victimization (score $\geq$ 16). Children with a high score in victimization and high scores only in relational aggression were not included.
(d) Control group – This group comprises children with a low frequency of direct aggressive behavior (score $\leq$ 7) and victimization with a low (score $\leq$ 12) or moderate (score $<$ 16) frequency.

Evaluation of Executive Functioning

The protocol for the analysis of cold executive functions used the model proposed by Diamond (2013). In this model, three main cores are part of executive functioning: inhibitory control, working memory, and cognitive flexibility. These three functions give rise to the other functions, such as reasoning, planning, and organization. The following instruments were used.

Digit Span Backward (DSB) Subtest (Wechsler, 2013)

A subtest of the Wechsler Intelligence Scale for Children (WISC-IV), the DSB evaluates working memory. For this task, the professional applying the test reads some numbers aloud, and the child must repeat them in descending order. The tables for 10 and 11 years of age were used to transform the raw scores into weighted scores.

Trail Making Test Part B (TMT-B)

The TMT has two parts: A and B. This study used only part B, which evaluates alternating attention and mental flexibility. The child was instructed to connect the numbers in ascending order and in alphabetical order. The execution time of the activity was considered to determine the score. When there was an error, the evaluator showed it to the participant and requested correction, which increased the execution time.

Victoria Stroop Color-Word Test

The Stroop Test was used to assess attention and inhibitory control. The Victoria version includes three cards, 1 (color), 2 (word), and 3 (color-word). The first card (color) contains colored rectangles with the colors pink, green, blue, and brown, which must be named by the child as quickly as possible. The second card (word) lists the words EACH, TODAY, NEVER, and EVERYTHING, printed in the same colors, and the child is asked to simply read the words as quickly as possible. The third card (color-word) lists the names of the four colors, printed in colors that are incompatible with the written word (e.g., the word "Blue" is printed in pink). The child is asked not to read the names but instead to name the printed colors as quickly as possible. For the assessment, the execution time for each card and the number of mistakes (errors not spontaneously corrected by the child) were taken into account (Kulaif, 2005).

For the assessment of the "hot" executive functions, the test of affective decision-making described below was used.

Iowa Gambling Task (IGT; Bechara et al., 1994)

The Brazilian version of the IGT, adapted by Malloy-Diniz et al. (2008), was used to evaluate hot executive functions as a test of emotional decision-making. In this task, participants aim to achieve the maximum gain from an initial cash loan. Individuals make 100 selections of cards, not knowing in advance how many are allowed, and they must make decisions that lead to a final positive result according to the feedback that they receive. Card decks A and B initially offer an advantage, but in the long term, they become unfavorable. Decks C and D offer an overall

advantage because, although they have a lower value of rewards, the punishments are also smaller, ultimately resulting in a higher overall gain.

In this study, to increase the chances that the test evaluated hot executive functions, a reward (candy) was included, according to the following criteria:

- Gains of 25, 50, and 75 (frequent in advantageous decks): receives one piece of candy;
- Losses of 25, 50, and 75 (frequent in advantageous decks): loses one piece of candy;
- Gains $\geq$ 100 (frequent in disadvantageous decks): receives two pieces of candy;
- Losses $\geq$ 100 (frequent in disadvantageous decks): loses two pieces of candy; and
- Losses = 1500 (only in disadvantageous decks): loses all candy.

Procedures

After approval by the school and parents by means of agreement documents and free and informed consent forms, the groups were determined by applying the PAVS. For the individual step, tests for the assessment of executive functioning were applied in an isolated room arranged by the school. The professional applying the test was with the child throughout task execution to answer questions and prevent mistakes due to confusion.

The study was approved by the Research Ethics Committee of the University Hospital Lauro Wanderley (Hospital Universitário Lauro Wanderley), UFPB (CAAE process: 17883413. 5.0000.5183). All procedures were performed according to Regulation 466/96 of the National Health Council (Conselho Nacional de Saúde – CNS). Participation was voluntary, and the participants were informed in advance that they could withdraw their consent at any time during the study.

Statistical Analysis

The softwares SPSS 21.0 and Microsoft Office Excel 2007 were used for the tabulation of data and statistical analysis. The Shapiro–Wilk test and Levene's test showed that data did not present normal distribution and equality of variances (homoscedasticity), respectively. For this reason, non-parametric testing was selected. The Kruskal–Wallis test was used for comparisons between groups using a significance level of 0.05. When Kruskal–Wallis test was inferior to 0.05, we performed Mann–Whitney pairwise comparisons. In order to control the probability of Type I error, we corrected the critical value of alfa by dividing the familywise error rate (0.05) by the number of comparisons (6). Therefore, we considered as statistically significant only the probabilities values inferior to 0.0083.

In addition, we determined effect sizes estimates (Fritz et al., 2012; Field, 2013). As proposed by Cohen (1988), effect sizes were calculated using the formula:

$$r = \frac{z}{\sqrt{N}} \quad (1)$$

where r is the effect size estimate, z is the standard score of the distribution, and N is the total of the sample size.

According to Cohen's guidelines used to interpret r, a large effect is superior to 0.5, a medium effect is 0.3 and a small effect is 0.1. Large effect sizes associated to non-significant results may suggest to carry out a research with a greater power, whereas small effect sizes associated to significant results may indicate that the observed effects are not so robust (Fritz et al., 2012).

RESULTS

With regard to socio demographic characteristics, a total of 32 out of the 60 children who participated in the sample were female, and 28 were male, with 34 attending private schools and 26 attending public schools in João Pessoa, Paraíba, Brazil.

The participants were divided into four groups according to their result on the PAVS scale: bullies (n = 15; seven male), victims (n = 15; six male), bully-victims (n = 15; nine male), and control (n = 15; six male). A preliminary statistical analysis showed no differences between genders with regard to the variables investigated in the study ($p > 0.05$). **Table 1** shows the average score of the four groups in the dimensions of the PAVS scale. In **Table 2**, we present data of the four groups of participants and results of the statistical analysis.

Strengths and Difficulties Questionnaire – SDQ

We found no differences between groups with regard to the total score of difficulties ($\chi^2 = 1.088$, $p = 0.780$), emotional problems ($\chi^2 = 6.585$, $p = 0.086$), hyperactivity ($\chi^2 = 1.087$, $p = 0.780$), conduct problems ($\chi^2 = 2.517$, $p = 0.472$) and peer relationship problems ($\chi^2 = 6.920$, $p = 0.740$). In the prosocial behavior subscale, we found differences between groups ($\chi^2 = 11.347$, $p = 0.01$). Mann–Whitney tests showed that victims presented higher scores than bullies ($U = 33.00$, $z = -3.217$, $p = 0.001$, $r = -0.59$), but not in comparison to the control group ($U = 73.5$, $z = -1.703$; $p = 0.089$, $r = -0.31$) and bully-victims ($U = 54.5$, $z = -2.495$; $p = 0.013$, $r = -0.46$). Bullies, bully-victims and controls had similar scores in prosocial behavior compared one another.

Digit Span Backward (DSB) Subtest

There was no significant difference between the groups with regard to DSB ($\chi^2 = 2.587$, $p = 0.46$), indicating that they had similar patterns of performance in working memory.

Trail Making Test Part B (TMT-B)

Statistical analysis showed significant differences between groups in TMT-B ($\chi^2 = 13.839$, $p = 0.003$). Mann–Whitney tests showed that the victim group had a longer execution time in TMT-B compared to bullies ($U = 32.5$, $z = -3.322$; $p = 0.001$, $r = -0.61$), but not differed from bully-victims ($U = 65$, $z = -1.972$, $p = 0.049$, $r = -0.36$), and controls ($U = 62.5$, $z = -2.075$, $p = 0.038$, $r = -0.38$). This result indicates a lower cognitive flexibility in the victim group. The other groups did not differ one another: aggressors compared to bully-victims ($U = 66$, $z = -1.932$, $p = 0.053$, $r = -0.35$); bullies compared to controls ($U = 66$, $z = -1.93$, $p = 0.054$, $r = -0.35$); bully-victims

TABLE 1 | Means and standard deviations of age and scores in the PAVS scale dimensions in the four groups of participants.

Variable	Bully	Victim	Bully-Victim	Control
Age	10.73 (0.45)	10.87 (0.35)	10.80 (0.41)	10,73 (0.45)
Relacional aggression	8.20 (4.29)	5.93 (1.62)	8.53 (3.29)	4.87 (1.12)
Direct aggression	11.73 (2.01)	6.47 (0.91)	12.67 (1.71)	6.40 (1.18)
Victimization	13.33 (2.19)	20.73 (4.90)	23.73 (5.78)	11.07 (2.05)

TABLE 2 | Statistical analysis and scores obtained by the four groups of participants in the Strengths and Difficulties Questionnaire (SDQ), Digit Span Backward Subtest (DSB), Trail Making Test part B (TMT-B), Victoria Stroop Color-Word Test (STROOP), Iowa Gambling Task (IGT).

Instrument	Bully	Victim	Bully-Victim	Control	Kruskal–Wallis
SDQ					
Emotional symptoms	3.53 (2.26)	5.80 (3.07)	3.27 (2.86)	4.00 (2.77)	$p = 0.086$
Conduct problems	3.07 (2.65)	1.87 (1.80)	2.73 (1.43)	2.27 (1.62)	$p = 0.472$
Hyperactivity	4.60 (3.26)	3.53 (2.10)	4.33 (1.91)	3.93 (2.89)	$p = 0.780$
Peer relationship Problems	1.53 (1.72)	2.67 (1.63)	2.47 (2.56)	1.20 (1.01)	$p = 0.074$
Prosocial behavior	7.07 (2.40)	9.27 (0.96)	7.87 (1.59)	8.33 (1.54)	$p = 0.010$*
Total difficulties	12.80 (8.24)	14.07 (7.16)	12.80 (6.71)	11.40 (5.27)	$p = 0.780$
DSB	9.33 (2.52)	9.53 (2.35)	9.93 (1.94)	8.73 (2.12)	$p = 0.460$
TMT-B	40.27 (10.27)	61.40 (17.31)	48.60 (12.43)	48.20 (11.91)	$p = 0.003$*
STROOP					
Color (Time)	16.00 (0.92)	19.13 (0.89)	18.58 (1.21)	17.80 (1.03)	$p = 0.126$
Color (Errors)	0.00 (0.00)	0.07 (0.26)	0.00 (0.00)	0.13 (0.352)	$p = 0.284$
Word (Time)	11.27 (3.41)	12.40 (2.41)	12.26 (2.68)	12.67 (2.58)	$p = 0.205$
Word (Errors)	0.07 (0.26)	0.00 (0.00)	0.13 (0.51)	0.07 (0.26)	$p = 0.792$
Color-word (Time)	27.47 (1.68)	34.20 (3.25)	35.21 (2.76)	30.40 (1.84)	$p = 0.018$*
Color-word (Errors)	0.40 (0.63)	0.27 (0.59)	0.47 (1.12)	0.60 (1.24)	$p = 0.869$
IGT					
Deck A choices	25.15 (0.74)	22.60 (1.29)	20.79 (0.96)	21.07 (1.26)	$p = 0.039$*
Deck B choices	27.33 (1.55)	27.53 (1.29)	30.13 (1.60)	29.47 (1.57)	$p = 0.286$
Deck C choices	25.00 (1.17)	25.00 (0.99)	26.47 (1.04)	24.53 (0.66)	$p = 0.325$
Deck D choices	24.00 (1.82)	24.87 (1.94)	21.73 (1.37)	24.93 (1.57)	$p = 0.566$
General Trend Block 1 (1–20)	−0.93 (0.64)	−1.47 (0.74)	−1.47 (0.90)	−1.07 (0.54)	$p = 0.971$
General trend block 2 (21–40)	−1.20 (0.95)	−0.40 (1.58)	−3.07 (1.53)	−1.47 (0.71)	$p = 0.859$
General trend block 3 (41–60)	−0.27 (0.67)	1.47 (1.75)	−2.00 (1.08)	1.07 (1.40)	$p = 0.697$
General trend block 4 (61–80)	−0.13 (1.50)	−0.93 (1.24)	0.80 (1.59)	−0.67 (1.11)	$p = 0.640$
General trend block 5 (81–100)	0.53 (0.95)	1.07 (0.93)	2.13 (1.38)	1.07 (1.18)	$p = 0.995$
General trend	−2.00 (3.20)	−0.27 (3.95)	−3.60 (3.48)	−1.07 (3.03)	$p = 0.881$

Values correspond to means and standard deviations.

compared to controls ($U = 109.5$, $z = -0.125$, $p = 0.901$, $r = -0.02$; **Figure 1**).

Stroop Color-Word Test

The Kruskal–Wallis test showed significant differences between groups only for the third card (color-word; $\chi^2 = 10{,}039$, $p = 0.018$). Mann–Whitney tests showed that the bully group had a shorter execution time compared to the victim ($U = 35$, $z = -2.736$, $p = 0.006$, $r = -0.50$) and bully-victim groups ($U = 31$, $z = -2.754$, $p = 0.006$, $r = -0.50$), but not differed from control group ($U = 52$, $z = -2.109$, $p = 0.035$, $r = -0.39$; **Figure 2**). In the third card, we found no differences between victims compared to bully-victims ($U = 87$, $z = -0.195$, $p = 0.846$, $r = 0.04$); victims compared to controls ($U = 93$, $z = -0.525$, $p = 0.600$, $r = 0.10$); bully-victims compared to controls ($U = 83$, $z = -0.669$, $p = 0.503$, $r = 0.12$). For the first card (color), we found no statistically significant differences between groups ($\chi^2 = 5.718$; $p = 0.126$), but victims presented longer execution time than other groups. We find no differences between groups with regard to Stroop word (time; $\chi^2 = 4.587$, $p = 0.205$), Stroop color (errors; $\chi^2 = 3.795$, $p = 0.284$), Stroop word (errors; $\chi^2 = 1.037$, $p = 0.792$), and Stroop color-word (errors; $\chi^2 = 0.718$, $p = 0.869$) (**Figure 2**).

Iowa Gambling Task – IGT

The Kruskal–Wallis test showed significant differences between groups only for choices from Deck A ($\chi^2 = 8{,}393$, $p = 0.039$). Mann–Whitney tests showed that the bully group had the highest score considering all choices from Deck A compared to the bully-victim group ($U = 34.5$ $z = -2.755$, $p = 0.006$, $r = 0.50$), but not differed from victims ($U = 61.5$ $z = -1.666$, $p = 0.96$, $r = 0.30$) and the control group ($U = 49$, $z = -2.246$, $p = 0.025$, $r = 0.41$).

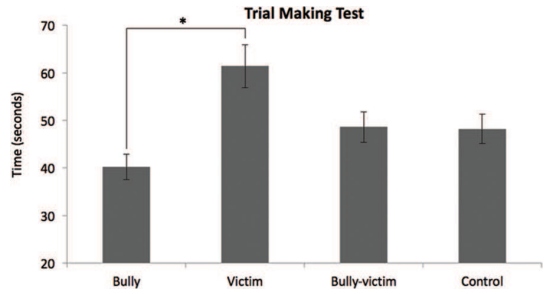

FIGURE 1 | Time, in seconds, on the Trail Making Test Part B (TMT-B). *Significant difference for the victim group compared to the bully group ($p = 0.001$).

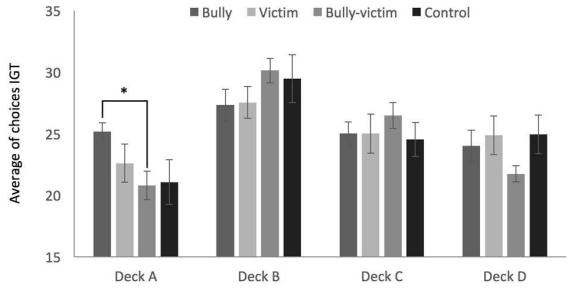

FIGURE 3 | Average of choices from decks A, B, C, and D on the Iowa Gambling Task (IGT). *Significant difference for the bully group compared to the bully-victim group in Deck A ($p = 0.006$).

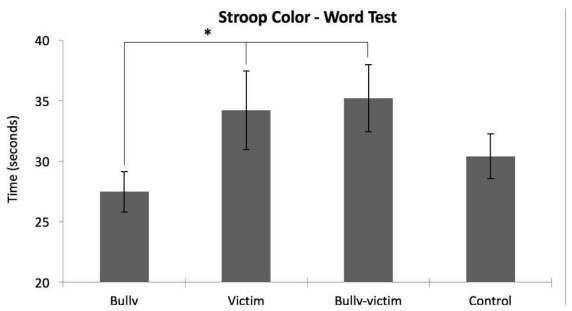

FIGURE 2 | Time, in seconds, on the Stroop Color-Word Test. *Significant difference for the bully group compared to victim ($p = 0.006$) and bully-victim ($p = 0.006$).

Other groups had a similar number of choices of cards in Deck A: victims compared to bully-victims ($U = 82$, $z = -1.006$, $p = 0.314$, $r = 0.18$); victims compared to controls ($U = 94$, $z = -0.771$, $p = 0.440$, $r = 0.14$); bully-victims compared to controls ($U = 99.50$, $z = -0.241$, $p = 0.810$, $r = 0.04$). There was no significant differences between the groups with regard to the general score trends in blocks ($\chi^2 = 0.241$, $p = 0.971$ in Block 1; $\chi^2 = 0.758$, $p = 0.859$ in Block 2; $\chi^2 = 1.435$, $p = 0.697$ in Block 3; $\chi^2 = 1.685$, $p = 0.640$ in Block 4, and $\chi^2 = 0.096$, $p = 0.995$ in Block 5) and the overall general trend ($\chi^2 = 0.668$, $p = 0.881$). There was also no difference between the total number of choices from Decks B ($\chi^2 = 3.780$, $p = 0.286$), C ($\chi^2 = 3.466$, $p = 0.325$), and D ($\chi^2 = 2.031$, $p = 0.566$) (**Figure 3**).

DISCUSSION

In this study, executive functioning (inhibitory control, working memory, and cognitive flexibility) and emotional decision-making were assessed in children who experience bullying. This study is innovative because it investigates multiple components of executive functioning and their relationship to bullying.

We used the Strengths and Difficulties Questionnaire – SDQ (parent version) to characterize chid behavior. In the SDQ, offending children (bullies) did not differ from other groups with regard to the symptoms of hyperactivity and behavior problems, contradicting the results of Coolidge et al. (2004), which found a higher prevalence of challenging behavior, conduct problems and ADHD in offending children compared to the control group. Therefore, it is clear that aggressors of this sample did not differ from controls with respect to behavior problems, probably due to this group presenting many children who also had average levels of victimization. Viding et al. (2011) claim that not all behavior problems are due to the same cause, so it is important to investigate the profile of each group.

The group of victims obtained the highest score of prosocial behavior, related to behaviors of empathy (helping others, being nice, and caring for younger children) than the group of bullies. However, there were no differences between victims compared to controls and bully-victims.

Deficits in executive functioning have been reported in several developmental and behavioral disorders (Lezak, 1982; Hamdan and Pereira, 2009). In this study, there was no significant difference between groups with regard to working memory, assessed by DSB Subtest. With regard to working memory, Best et al. (2002) found no differences between patients with aggressive and impulsive behavior compared to controls. Nevertheless, they observed that the clinical group showed impairment in the decision-making process.

Contrary to expectations, there was no deficit in inhibitory control functions and cognitive flexibility in bullies, as assessed by the Stroop test and TMT-B, respectively. The bully group had a shorter execution time on the TMT-B compared to the victims group and the third Stroop card (color-word) compared to the victims and bully-victims groups and not presented more errors. Brennan (2002) found no association between high levels of juvenile delinquency and poor performance in the executive function assessment tasks. However, our results are different from those reported by other authors who observed inhibitory control difficulties in aggressive individuals (Best et al., 2002; Ellis et al., 2009). Verlinden et al. (2014) found a relationship between low inhibitory control and involvement in bullying, whether in the bully, victim or bully-victim roles. Nevertheless, the authors used an indirect assessment with questionnaires directed to parents, which may explain the difference between the results. Compared to bullies, the victim group had a longer TMT-B execution time, indicating less efficient performance in

the context of cognitive flexibility. Although not statistically significant, we found medium effect sizes to the comparisons between victims and bully-victims ($r = 0.36$) and between victims and controls ($r = 0.38$), what indicates a reduction in cognitive flexibility in victims compared to those groups. This result is consistent with those found by Dertelmann (2011), who found lower performance in cognitive flexibility tests and working memory in child victims of abuse (Dertelmann, 2011). Brennan (2002) found that children who had suffered abuse and higher delinquency levels had lower scores on the assessment of executive functioning. This result shows that the presence of victimization is a factor that may be associated with deficits in the development of cognitive impairment. Other studies also show worse performance in tasks that assess executive functioning in individuals who have suffered physical or sexual assaults (Stein et al., 2002; Coolidge et al., 2004).

The association between deficits in executive functioning and vulnerability to aggression can be explained as a consequence of exposure to violence, but it can also be understood as a factor of vulnerability to such acts. The different types of victimization investigated and the lack of longitudinal studies do not allow us to safely determine whether impairment in executive functioning is a result of aggression, whether it is associated with psychiatric disorders developed due to aggression (anxiety disorders, post-traumatic stress disorder), or whether it is part of the cognitive and personality features of these individuals, which may predispose them to suffer aggression (Stein et al., 2002). According to Teicher et al. (2003), exposure to violence or severe stress in childhood, depending on its severity and intensity, can cause neurobiological changes and affect brain development. For example, Johnson (2012) suggests that the presence of deficits in executive functioning since childhood can make individuals less efficient in problem solving and, therefore, less resilient in adverse situations.

In this study, compared with the bully-victim group, children in the bully group choose more cards from one of the disadvantageous decks (Deck A). Decks A and B are considered disadvantageous because they cause losses over the long term of task execution compared to decks C and D. Although deck B is also unfavorable, Deck A has the highest frequency of punishments but is lower in intensity (Singh, 2013). We found no statistically significant differences between bullies and controls in IGT, however, the effect size obtained in the comparison (0.41) indicates that groups might differ each other in studies involving a greater sample, with bullies choosing more disadvantageous cards.

This finding suggests that bullies are more sensitive to the intensity of punishment than they are to the frequency of punishment. The choice for one of the unfavorable decks by bullies indicates a preference for immediate gains (two pieces of candy), ignoring punishment and the future consequences of the choice. Such behavior has been designated "myopia for the future" (Bechara et al., 1994, 2002; Gomes et al., 2011).

With regard to "myopia for the future," the following analogy can be made for a situation experienced at school: a child can choose between advantageous attitudes (not attacking), which generate long-term gains (e.g., being aware of doing the right thing, building lasting and true friendships), and unfavorable behavior (aggression), which brings immediate gains (a sense of power, entertaining peers, being popular) but generate losses in the long run (complaints, punishment by parents, poor school performance, and shallow friendships). In this sense, it is possible to consider that the practice of bullying in the school context may be associated with a decrease in the decision-making process of bullies. Decision-making deficits are clearly found in children and adolescents with behavioral disorders, conduct disorders and in patients who suffered injuries to the orbitofrontal cortex (Best et al., 2002; Ernst et al., 2003; Fairchild et al., 2009).

Bully-victims present similarities and differences with regard to both groups of victims and bullies. In the IGT, bully-victims were similar to controls and victims, but choose more advantage cards as compared to bullies. In SQD, bully-victims presented scores of prosocial behavior more similar to bullies than victims. A possible explanation is that the decreasing of prosocial behavior in bully-victims may be related to the dissemination of the aggression suffered. For Bandeira and Hutz (2010), bully-victims children are more likely to present depressive symptoms, anxiety, and externalizing behaviors, and unlike children in the bullies group, they are not popular but rather rejected by their peers.

The results of this study can be analyzed by considering the dichotomy proposed by Kerr and Zelazo (2004). These authors suggest the existence of hot (more closely related to motivation and emotional control) and cold (more closely related to logical-rational aspects of cognition) executive functions. If, on one hand, victims have experienced greater difficulties in tasks that require cold executive functions, then bullies have impaired "hot" executive functions.

This study includes certain limitations, such as the sample size and the fact that some children in the bully group have shown moderate levels of victimization. Another limitation of the study is the use of a self-reported scale, which can generate interference in the division of the groups, although this problem was minimized by the application of the ICU scale in children and parents. It should also be considered that the methodology used was transversal and causal inferences about the investigated aspects cannot be made. We suggest that future studies be conducted with larger samples, longitudinal studies and different cultures.

In addition to sociocultural variables, this study shows that executive functioning, including decision-making, can also play a relevant role in bullying behavior. This type of study may lead to the development of customized intervention strategies according to the profile of students in each school because not all behavioral issues are due to the same cause and not every victim responds to aggression in the same manner (Viding et al., 2011).

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: WM, NT-A, and CM. Performed the experiments: WM. Analyzed the data: WM, NT-A, and CM. Contributed with materials and analysis tools: WM, NT-A, CM, and LM-D. Wrote the paper: WM, NT-A, CM, and LM-D.

REFERENCES

Bandeira, C. M., and Hutz, C. S. (2010). As implicações do bullying na auto-estima de adolescentes. *Psicol. Esc. Educ.* 14, 131–138. doi: 10.1590/S1413-85572010000100014

Bandeira, C. D. M., and Hutz, C. S. (2012). Bullying: prevalence, implications and gender differences. *Psicol. Esc. Educ.* 16, 35–44. doi: 10.1590/S1413-85572012000100004

Bechara, A., Damásio, A. R., Damásio, H., and Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50, 7–15. doi: 10.1016/0010-0277(94)90018-3

Bechara, A., Dolan, S., and Hindes, A. (2002). Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia* 40, 1690–1705. doi: 10.1016/S0028-3932(02)00016-7

Berger, K. S. (2007). Update on bullying at school: science forgotten? *Dev. Rev.* 27, 90–126. doi: 10.1016/j.dr.2006.08.002

Best, M., Williams, J. M., and Coccaro, E. F. (2002). Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder. *Proc. Natl. Acad. Sci. U.S.A.* 99, 8448–8453. doi: 10.1073/pnas.112604099

Brennan, S. G. C. (2002). *The Relationship between Maltreatment in Childhood and Delinquency: An Examination of IQ and Executive Functions*. Palo Alto, CA: Pacific Graduate School of Psychology.

Bullock, J. (2002). Bullying Among Children. *Child. Educ.* 78, 130–133. doi: 10.1080/00094056.2002.10522721

Camodeca, M., and Goossens, F. A. (2005). Aggression, social cognitions, anger and sadness in bullies and victims. *J. Child Psychol. Psychiatry* 46, 186–197. doi: 10.1111/j.1469-7610.2004.00347.x

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences,* 2nd Edn. Hillsdale, NJ: Lawrence Earlbaum Associates.

Coolidge, F. L., DenBoer, J. W., and Segal, D. L. (2004). Personality and neuropsychological correlates of bullying behavior. *Pers. Individ. Dif.* 36, 1559–1569. doi: 10.1016/j.paid.2003.06.005

Cunha, J. M., Weber, L. N. D., and Steiner Neto, P. (2009). "Escala de vitimização e agressão entre pares (EVAP)," in *Pesquisando em Família - Instrumentos Para Coleta e Análise de Dados*, eds L. Weber and M. A. Dessen (Curitiba: Juá Editora), 108–120.

Damásio, A. (1996). *O erro de Descartes: Emoção, Razão e o Cérebro Humano*. São Paulo: Companhia das Letras.

Damásio, A. R., Everitt, B. J., and Bishop, D. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 351, 1413–1420. doi: 10.1098/rstb.1996.0125

Dertelmann, C. D. F. V. (2011). *Avaliação Neuropsicológica em Crianças Vítimas de Maus-Tratos*, Dissertação de mestrado, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre.

DeVito, E. E., Blackwell, A. D., Kent, L., Ersche, K. D., Clark, L., Salmond, C. H., et al. (2008). The effects of methylphenidate on decision making in attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 64, 636–639. doi: 10.1016/j.biopsych.2008.04.017

Diamond, A. (2013). Executive functions. *Annu. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

Ellis, M. L., Weiss, B., and Lochman, J. E. (2009). Executive functions in children: associations with aggressive behavior and appraisal processing. *J. Abnorm. Child Psychol.* 37, 945–956. doi: 10.1007/s10802-009-9321-5

Ernst, M., Grant, S. J., London, E. D., Contoreggi, C. S., Kimes, A. S., and Spurgeon, L. (2003). Decision making in adolescents with behavior disorders and adults with substance abuse. *Am. J. Psychiatry* 160, 33–40. doi: 10.1176/appi.ajp.160.1.33

Ernst, M., Luckenbaugh, D. A., Moolchan, E. T., Temple, V. A., Jenness, J., Korelitz, K. E., et al. (2010). Decision-making and facial emotion recognition as predictors of substance-use initiation among adolescents. *Addict. Behav.* 35, 286–289. doi: 10.1016/j.addbeh.2009.10.014

Fairchild, G., van Goozen, S. H. M., Stollery, S. J., Aitken, M. R. F., Savage, J., Moore, S. C., et al. (2009). Decision making and executive function in male adolescents with early-onset or adolescence-onset conduct disorder and control subjects. *Biol. Psychiatry* 66, 162–168. doi: 10.1016/j.biopsych.2009.02.024

Field, A. (2013). *Discovering Statistics Using IBM SPSS Statistics*. Thousand Oaks, CA: Sage Publications.

Fleitlich, B., Cortázar, P. G., and Goodman, R. (2000). Questionário de capacidades e dificuldades (SDQ). *Infanto Rev. Neuropsiquiatria Infânc. Adolescênc.* 8, 44–50.

Fritz, C. O., Morris, P. E., and Richler, J. J. (2012). Effect size estimates: current use, calculations, and interpretation. *J. Exp. Psychol. Gen.* 141, 2–18. doi: 10.1037/a0024338

Gery, I., Miljkovitch, R., Berthoz, S., and Soussignan, R. (2009). Empathy and recognition of facial expressions of emotion in sex offenders, non-sex offenders and normal controls. *Psychiatry Res.* 165, 252–262. doi: 10.1016/j.psychres.2007.11.006

Gini, G. (2006). Social cognition and moral cognition in bullying: what's wrong? *Aggress. Behav.* 32, 528–539. doi: 10.1002/ab.20153

Gomes, F., Mata, F. S. N., Lage, G. M., Paiva de Moraes, P. H., Moraes, P., Fuentes, D., et al. (2011). Avaliação neuropsicológica do processo de tomada de decisões em crianças e adolescentes: uma revisão integrativa da literatura. *Rev. Psiquiatr. Clín.* 38, 106–115.

Goodman, R. (1997). The strengths and difficulties questionnaire: a research note. *J. Child Psychol. Psychiatry* 38, 581–586. doi: 10.1111/j.1469-7610.1997.tb01545.x

Hamdan, A. C., and Pereira, A. P. D. A. (2009).Neuropsychological assessment of executive functions: Methodological questions. *Psicol. Reflexão E Crít.* 22, 386–393. doi: 10.1590/S0102-79722009000300009

Herrera, G. M. (2011). Bulimia nervosa: emotions and making decisions. *Rev. Psiquiatr. Salud Ment.* 4, 88–95. doi: 10.1016/j.rpsm.2011.03.002

Johnson, M. H. (2012). Executive function and developmental disorders: the flip side of the coin. *Trends cogn. sci.* 16, 454–457. doi: 10.1016/j.tics.2012.07.001

Kerr, A., and Zelazo, P. D. (2004). Development of "hot" executive function: the children's gambling task. *Brain Cogn.* 55, 148–157. doi: 10.1016/S0278-2626(03)00275-6

Koh, J. B., and Wong, J. S. (2015). Survival of the fittest and the sexiest: evolutionary origins of adolescent bullying. *J. Interpers. Violence* doi: 10.1177/0886260515593546 [Epub ahead of print].

Kulaif, T. (2005). *O Teste de Cores e Palavras de Stroop Modificado Para Analfabetos,* Dissertação de mestrado, Universidade de São Paulo, São Paulo.

Lezak, M. D. (1982). The problem of assessing executive functions. *Int. J. Psychol.* 17, 281–297. doi: 10.1080/00207598208247445

Lopes Neto, A. A. (2005). Bullying: comportamento agressivo entre estudantes. *J. Pediatr.* 81, 164–172. doi: 10.1590/S0021-75572005000700006

Malloy-Diniz, L. F., Leite, W. B., Moraes, P. H. P. de Correa, H., Bechara, A., and Fuentes, D. (2008). Brazilian portuguese version of the iowa gambling task: transcultural adaptation and discriminant validity. *Rev. Bras. Psiquiatr.* 30, 144–148. doi: 10.1590/S1516-44462008005000009

Mata, F. G. D., Neves, F. S., Lage, G. M., Moraes, P. H. P. D., Mattos, P., Fuentes, D., et al. (2011). Neuropsychological assessment of the decision making process in children and adolescents: an integrative review of the literature. *Arch. Clin. Psychiatry* 38, 106–115. doi: 10.1590/S0101-60820110000300005

Medeiros, W. M. B., Moita Minervino, C. A. S., Duarte, J. S., Cavalcanti, J. D. T., and Alves, N. T. (2014). Competência emocional e bullying: uma visão da neurociência. *Pediatr. Mod.* 50, 100–110.

Miranda, R. D. S. (2011). *Bullying a Partir de Representações Sociais De Estudantes,* Dissertação de Mestrado, Universidade Federal da Paraíba, João Pessoa.

Olweus, D. (1994). *Bullying at School*. NewYork, NY: Springer.

Sallum, I., Mata, F., Miranda, D. M., and Malloy-Diniz, L. F. (2013). Staying and shifting patterns across IGT trials distinguish children with externalizing disorders from controls. *Front. Psychol.* 4:899. doi: 10.3389/fpsyg.2013.00899

Séguin, J. R. (2004). Neurocognitive elements of antisocial behavior: relevance of an órbito-frontal cortex account. *Brain Cogn.* 55, 185–197. doi: 10.1016/S0278-2626(03)00273-2

Sinclair, S., and Gansler, D. (2006). Integrating the somatic marker, and social cognition theories to explain different manifestations of antisocial personality. *New School Psychol. Bull.* 4, 25–47.

Singh, V. (2013). A potential role of reward and punishment in the facilitation of the emotion-cognition dichotomy in the iowa gambling task. *Front. Psychol.* 4:944. doi: 10.3389/fpsyg.2013.00944

Smith, P. K. (2002). "Intimidação por colegas e maneiras de evitá-la," in *Violência nas Escolas e Políticas Públicas,* eds E. Debarbieux and C. Blaya (Brasilia: Unesco), 187–205.

Smith, P. K., and Jones, A. P. (2012). The importance of developmental science for studies in bullying and victimization. *Int. J. Dev. Sci.* 6, 71–74. doi: 10.3233/DEV-2012-11093

Stein, M. B., Kennedy, C. M., and Twamley, E. W. (2002). Neuropsychological function in female victims of intimate partner violence with and without posttraumatic stress disorder. *Biol. Psychiatry* 52, 1079–1088. doi: 10.1016/S0006-3223(02)01414-2

Suhr, J. A., and Tsanadis, J. (2007). Affect and personality correlates of the iowa gambling task. *Pers. Individ. Dif.* 43, 27–36. doi: 10.1016/j.paid.2006.11.004

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., and Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neurosci. Biobehav. Rev.* 27, 33–44. doi: 10.1016/S0149-7634(03)00007-1

Tung, S., and Chhabra, N. (2011). A comparative study on the neuropsychological status of delinquent and non-delinquent boys. *Int. J. Cul. Ment. Health* 4, 121–127. doi: 10.1080/17542863.2010.530772

Verdejo-García, A., Pérez-García, M., and Bechara, A. (2006). Emotion, decision-making and substance dependence: a somatic-marker model of addiction. *Curr. Neuropharmacol.* 4, 17–31. doi: 10.2174/157015906775203057

Verlinden, M., Veenstra, R., Ghassabian, A., Jansen, P. W., Hofman, A., Jaddoe, V. W. V., et al. (2014). Executive function in gand non-verbal intelligence as predictors of bullying in early elementary school. *J. Abnorm. Child Psychol.* 42, 953–966. doi: 10.1007/s10802-013-9832-y

Viding, E., McCrory, E. J., Blakemore, S.-J., and Frederickson, N. (2011). Behavioural problems and bullying at school: can cognitive neuroscience shed new light on an old problem? *Trends Cogn. Sci*. 15 289–291. doi: 10.1016/j.tics.2011.05.001

Wechsler, D. (2013). *Escala de Inteligência Wechsler para Crianças- WISC-IV: Manual de instruções para aplicação e avaliação (1a edição)*. São Paulo: Casa do Psicólogo.

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The Relationship between Sleep Complaints, Depression, and Executive Functions on Older Adults

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Aim: In this manuscript, we report data on the association between executive functions screened by Frontal Assessment Battery, Five Digit Test and Digit Span with self-reported depressive symptoms and sleep complaints in non-demented older adults.

Methods: A total sample of 95 non-demented older adults performed Geriatric Depression Scale short version, Frontal Assessment Battery, Five Digit Test, Digit Span, and clinical interview. We split participants in groups stratified by age according to: young-old (60–69 years of age), old-old (70–79 years), and oldest-old (>80 years) and compared these three groups on the sociodemographic characteristics and executive functions performance. We carried out Poisson regression with robust error variance to verify sleep complaints and depression effects on executive functions performance. Gender, age, years of formal education, use of antidepressants and of benzodiazepines were considered as confounding variables, taking into account executive functions as dependent and sleep complaints and depression as independent variables.

Results: Controlling the effect of age, gender, years of formal education, use of benzodiazepines and of antidepressants there was a significant influence of depression in motor programming, inhibitory control, and working memory. Individuals without depression show motor programming scores 68.4% higher, inhibitory control scores 3 times greater and working memory scores also 3 times greater than individuals without depression. There was a significant influence of sleep complaints in phonemic fluency, motor programming, inhibitory control, and working memory. Individuals without sleep complaints show phonemic fluency scores 2 times greater than, motor programming scores 85.9% higher, inhibitory control scores 3 times greater and working memory scores also 3 times greater than individuals without sleep complaints.

Conclusions: Sleep complaints are associated with phonemic fluency, motor programming, inhibitory control, and working memory impairment. Depression symptoms presence are associated with motor programming and working memory performances. Depression and sleep complaints interaction would determine worse phonemic fluency, inhibitory control and working memory cognitive performance than these two conditions alone.

Keywords: sleep, executive function, depression, geriatrics, mild cognitive impairment, older adults, neuropsychological tests

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INTRODUCTION

Across the lifespan, sleep complaints are often comorbid with psychiatric disorders and are common in depression. Sleep has been studied extensively in this psychiatric disorder and were found objective, robust and relatively specific changes in sleep architecture related to neurobiology of depression (Benca and Peterson, 2008). On the present study, we provide a solid background for the importance of taking into account the interaction between cognition, sleep disorders, and depression among older adults.

During a depressive episode, cortical metabolic activity is increased in frontal areas, what impact sleep and cause subjective complaints of non-restorative sleep. In depressed patients, there is an imbalance of interaction between cholinergic and adrenergic mechanisms that promote abnormalities in sleep architecture (non-REM and REM). There are changes in non-REM sleep that result in excessive daytime sleepiness. Moreover, depressed patients exhibit cortisol and temperature desynchronization on advanced sleep phase (the expression of these rhythms appears earlier than expected) and on the sleep-wake cycle (Cajochen et al., 2001).

Processing speed (Bastien et al., 2003), executive functions such as switching, working memory, problem solving and inhibitory control (Nebes et al., 2009) and memory (Haimov et al., 2008), are associated with self-reported sleep complaints. Moreover, sleep disorders as self-reported change in sleep increases the risk of cognitive decline (Hahn et al., 2014).

Depression also increases susceptibility to cognitive decline and neurodegenerative dementia (Diniz et al., 2013), impact activities of daily living and patient quality of life, and rising health care costs. Among cognitive impairment associated with depression, executive function is the most prominent (Snyder, 2013), but deficits in processing speed (Jungwirth et al., 2011), spatial processing (Elderkin-Thompson et al., 2004), and verbal episodic memory (Nebes et al., 2000) are also found. They mediate decline in more complex functions such as attention, planning and problem solving. There is evidence of a close relationship between sleep loss, depression and cognition with effect sizes in "moderate range" (Lim and Dinges, 2010).

The aim of this study was to investigate the association between executive functions screened by Frontal Assessment Battery, Five Digit Test and Digit Span with comorbid self-reported depressive symptoms and sleep complaints in non-demented older adults. Overall, we hypothesized that sleep complaints and depression should be associated with executive functions impairment and that depression and sleep complaints interaction would determine a worse cognitive performance than these two conditions alone.

MATERIALS AND METHODS

Participants

We included a convenience sample of 95 older adults that were consecutively assessed at geriatric outpatient clinic at Belo Horizonte, Brazil between February 2011 and December 2015. These participants were visiting the clinic as a center of specialized geriatric treatments referred by other smaller primary care centers. The inclusion criteria were: age of 60 years or older. We excluded individuals that satisfied DSM-V and consensus criteria for dementia as NINCDS-ADRDA; individuals with major psychiatric comorbidities (e.g., bipolar disorder, schizophrenia, substance abuse); sensory disabilities that interfere with cognitive evaluation; neurodegenerative diseases of the central nervous system diagnosis (e.g., Parkinson's disease); clinical or historical evidence of transient ischemic attack or stroke or clinical instability. In the end, we have had a total of 175 participants. Of these 57 were excluded due to meet criteria for dementia due to Alzheimer's disease and 23 for dementia due to other etiologies such as frontotemporal and vascular dementia. Participants were instructed to perform tasks with the dominant hand. This study was approved by the local Ethics Committee (Belo Horizonte, MG) and all subjects agreed and signed the informed consent in accordance with the Declaration of Helsinki.

Neuropsychological Assessment

Neuropsychological assessments occurred between 08:00 a.m. and 05:00 p.m., then the time of day was not in a similar range for all the participants. There are evidence that cognitive performance may varies during the course of the day and reflect the level of alertness, which is determined by circadian rhythms (Schmidt et al., 2007). It is discussed that these findings can be attributed to underlying circadian and homeostatic factors. Different aspects of attention follow different time-of-day variations (Kraemer et al., 2000) and this bias was not controlled on the present study.

Diagnosis involved a clinical interview and a neuropsychological evaluation with a protocol previously validated for this population (de Paula et al., 2013a) composed by the following instruments: Mini Mental State Examination (MMSE) Brazilian version as a measure of general cognition; Clock Drawing Test as a measure of spatial processing, praxia, and executive functions; The Digit Span Task adapted from Wechsler Adult Intelligence Scale to assess short term memory; Corsi Blocks a measure of spatial short term memory; Semantic Verbal Fluency that measures the fluency component of the executive functions. Finally, Token Test-Short Version was used to assess language comprehension. Functional status was also assessed in the clinical interview using the caregivers' reports. Based on this evaluation, non-demented participants were invited for participation.

The MMSE were performed as a measure of general cognitive functioning and Activities of Daily Living (ADLs) inventory as a measure of functional status. Frontal Assessment Battery (FAB) Brazilian version was used to access executive functions. It presents a good validity for this population (de Paula et al., 2013b) and consists of six subtests which measures: Categorization, verbal fluency, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.

Depressive Symptoms Assessment

All the participants performed the short version (15-items) of the Geriatric Depression Scale (GDS-15) and we considered

the cutoff 6 (non-case/case) to classify presence/absence of significant depressive symptoms. To minimize low education bias, the scale was applied orally and the questions were repeated if requested by the participant. Depressive symptoms assessment was conducted on the same date of neuropsychological assessment and participant were required to answer according to how he felt in "last few weeks."

Sleep and Pharmacological Assessment

Sleep complaints was evaluated qualitatively through of a clinical interview with self report of participants. It was required to participants if they had noticed sleep-related problems in recent months or weeks to date. The response was evaluated in "yes/no" and they also describe the sleep problems.

The use of drugs, including benzodiazepines, was assessed by patients' medical records. Pharmacological treatments were evaluated during the anamnesis. Patients and caregivers reported which drugs were used at that time, and based on these data the drugs were classified as antidepressants or benzodiazepines. In the database the names of the drugs were specified, the number of medications in use and dichotomous variables were created for use of hypnotics and antidepressants.

Statistical Procedures

Once our data distribution was predominantly non-parametric, the statistical procedures were performed by non-parametric tests. Sociodemographic description and neuropsychological tests were performed through Mann–Whitney *U*-test for continuous variables and by Chi-Square for dummies variables.

We split participants in groups stratified by age according to: young-old (60–69 years of age), old-old (70–79 years), and oldest-old (>80 years) and we compared these three groups on the sociodemographic characteristics and executive functions performance through Kruskal–Wallis Test.

We carried out Poisson regression with robust error variance (McCullagh and Nelder, 1983) to verify depression and sleep complaints effects on executive functions performance. Gender, age, years of formal education use of antidepressants and of benzodiazepines were considered as confounding variables, taking into account executive functions as dependent and depression and sleep complaints, as independent variables. These statistical procedures were performed using SPSS 21.0. and statistical significance was established at 0.05.

RESULTS

The demographic description and neuropsychological tests performance are shown in **Table 1** for Chi-square analysis and in **Table 2** for Mann–Whitney. A total of 95 non-demented older adults $(60–91 years ($M = 74$, $SD = 7$), predominantly low formal education ($M = 5$, $SD = 4$) were enrolled in this study. In this sample, 36% were depressed, 48% with sleep complaints, 14% in use of benzodiazepines, and 23% of antidepressants including 15 participants in use of selective serotonin reuptake inhibitors (SSRI) and 7 in use of tricyclic antidepressant (TCA) (**Table 1**). No significant differences between age ($U = 1128.00$, $p = 0.407$), education ($U = 1069.00$, $p = 0.273$) or proportion of men and women ($\chi^2 = 0.024$, $p = 0.524$) were found between patients with and without sleep complaints. There is no difference between performance on Mini Mental State Examination between two conditions ($U = 594.00$, $p = 0.756$), daily function activities ($\chi^2 = 0.437$, $p = 0.358$), FAB total score ($U = 1177.00$, $p = 0.623$), or use of benzodiazepines ($\chi^2 = 2.248$, $p = 0.113$). Differences in presence of significant depressive symptoms classified through GDS-15 cutoff between groups with and without sleep complaints are found ($\chi^2 = 16.429$, $p < 0.001$) with more patients with depression in the group with sleep complaints.

In **Tables 3, 4** we could see descriptive statistics between age groups for socio-demographic variables and results of group comparisons between executive functions performance among non-demented elderly stratified by age. There are significant differences on categorization between young-old (60–69 years of age) and oldest-old (>80 years) ($\chi^2 = 18.479$, $p = 0.046$). Phonemic verbal fluency performance is significantly different between young-old (60–69 years of age) and old-old (70–79 years) ($\chi^2 = 17.280$, $p = 0.019$). In relation to motor programming there are differences between young-old (60–69 years of age) and old-old (70–79 years) ($\chi^2 = 19.000$, $p = 0.031$) and between young-old (60–69 years of age) and oldest-old (>80 years) ($\chi^2 = 24.750$, $p = 0.003$). Otherwise, performance on inhibitory control is only significantly different between old-old (70–79 years) and oldest-old (>80 years) ($\chi^2 = 19.910$, $p = 0.006$). For FAB total score, performance is significantly different between young-old (60–69 years of age) and old-old (70–79 years) ($\chi^2 = 17.557$, $p = 0.032$) and young-old (60–69 years of age) and oldest-old (>80 years) ($\chi^2 = 32.250$, $p > 0.001$).

In **Table 5** we present the Poisson regression to verify depression and sleep complaints effects on executive functions performance. Controlling the effect of age, gender, years of formal education, use of benzodiazepines and of antidepressants sleep complaints are associated with cognitive impairment on phonemic fluency, motor programming, inhibitory control and working memory. Individuals without sleep complaints have FAB motor programming scores 85.9% higher, phonemic fluency scores twice as high as, inhibitory control scores three times as high as and Digit Span Backward scores three times as high as individuals with sleep complaints.

Depression complaints is associated with motor programming and working memory impairment. Individuals without depression symptoms have FAB motor programming 68.4% higher and Digit Span Backward scores three times as high as individuals with depression symptoms.

Individuals without use of benzodiazepines presents sensitivity to interference scores six times as high as individuals in use of benzodiazepines. However, the use is associated with an increase of 19.2% on phonemic fluency scores. Individuals in use of antidepressants have motor programming scores 39.2% higher than individuals with no use of antidepressants.

Interaction between sleep and depression complaints is associated with phonemic fluency, inhibitory control and working memory impairment. Those which showed these two types of symptoms presents FAB fluency subtest scores 56.6%, FAB inhibitory control subtest scores 75% and Digit

TABLE 1 | Results of Chi-square Tests on gender, use of benzodiazepines and use of antidepressants proportion for participants with and without sleep complaints.

	Total sample (%)	Sleep complaints (%)	With no sleep complaints (%)	Groups comparison between participants with sleep complaints and without sleep complaints	
				X^2	*p*
Gender[a]	62	73	77	0.332	0.564
Benzodiazepines[b]	12	20	10	2.248	0.134
Antidepressants[c]	22	32	15	3.644	0.056
Depression	31	57	17	16.266	<0.001

[a]*Proportion of women.*
[b]*Proportion of use.*
[c]*Proportion of use.*

TABLE 2 | Group comparisons between participants with sleep complaints and without sleep complaints.

	Total sample			Sleep complaints			Without sleep complaints			Groups comparisons		
	M	*SD*	Range	*M*	*SD*	Range	*M*	*SD*	Range	MW-U	*Z*	*p*
Age	74.46	7.355	58–91	73.80	7.654	58–90	75.08	6.990	62–91	1128	−0.829	0.407
Education	5.68	4.865	0–22	5.21	4.964	0–22	6.12	4.853	0–21	1069	−1.096	0.273
MMSE	25.67	3.078	15–30	25.08	4.041	15–30	25.87	2.419	21–30	594	−0.311	0.756
FAB	12.23	3.281	4–18	12.14	3.380	4–18	12.48	3.245	6–18	1177	−0.492	0.623
ADL	3.63	4.834	0–23	3.86	4.740	0–18	2.91	4.568	0–23	542	−1.201	0.23

Values are frequencies or Mean ± Standard Deviation (SD); FAB, Frontal Assessment Battery; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living; MW-U, Mann–Whitney U-Test; Z, difference between standard scores; p, significance level.

TABLE 3 | Descriptive statistics between age groups for socio-demographic variables.

	Total sample	Age groups		
Age ranges	**60–91**	**Young–old 60–69**	**Old–old 70–79**	**Oldest–old >80**
N	95	24	47	24
Age	74.49 ± 7.29	65.54 ± 2.637	74.62 ± 2.75	83.88 ± 3.180
SEX				
Men	29	5	16	8
Woman	66	19	31	16
EDUCATION				
Years of formal education	5.71 ± 4.89	7.142 ± 5.174	5.78 ± 5.133	4.08 ± 3.538
Illiteracy	7	2	3	2
Primary school	65	14	34	20
Secondary or Higher	23	8	10	2
Pfeffer scale	3.400 ± 4.648	4.230 ± 4.206	2.760 ± 3.940	4.050 ± 6.013
MMSE	25.591 ± 3.083	27 ± 2.221	25.588 ± 2.664	25.000 ± 3.293

Values are frequencies or Mean ± Standard Deviation (SD); MMSE, Mini Mental State Examination.

Span Backward scores 70.1% lower than individuals with no complaints.

Sociodemographic variables are also associated with executive functions performances. At each year added on age, FAB conceptualization scores decreases 1.9%, sensitivity to interference scores decreases 2.2%, inhibitory control scores decreases 3.6%, FAB total scores decreases 1.5% and errors on Five Digit Test cognitive flexibility task increases 3.5%. At each year added on formal education, FAB conceptualization scores increases 5.3%, phonemic verbal fluency scores increases 3.2%, motor programing scores increases 2.1%, FAB total scores increases 1.6% and Digit Span Backward scores increases 6.1%. Female individuals have FAB total scores 1.7% higher than the males (**Table 5**).

TABLE 4 | Results of group comparisons between executive functions performance among non-demented elderly stratified by age.

	Total sample	Age groups			Group comparisons		
		1—Young-Old	2—Old-Old	3—Oldest-Old	X^2	*p*	Differences between age groups
Age ranges	**60–91**	**60–69**	**70–79**	**>80**			
FAB (total score)	12.32 ± 3.294	14.33 ± 2.353	12.34 ± 3.171	10.54 ± 3.148	17.557	0.032	2 > 3
					32.250	<0.001	1 > 3
FAB—categorization	1.505 ± 1.071	1.958 ± 0.908	1.456 ± 1.110	1.208 ± 1.021	18.479	0.046	1 > 3
FAB—fonemic fluency	2.147 ± 0.989	2.625 ± 0.711	1.978 ± 1.022	2.083 ± 0.974	17.280	0.019	1 > 2
FAB—motor programming	1.726 ± 0.950	2.042 ± 0.806	1.782 ± 0.987	1.333 ± 0.917	19.000	0.031	1 > 2
					24.750	0.003	1 > 3
FAB—sensitivity to interference	2.357 ± 1.051	2.708 ± 0.751	2.326 ± 1.097	2.083 ± 1.176	2.988	0.131	–
FAB—inhibitory control	1.589 ± 1.180	2.000 ± 1.142	1.782 ± 1.153	0.875 ± 0.947	19.910	0.006	2 > 3
Five digit test inhibitory control	3.730 ± 5.535	2.940 ± 5.048	3.360 ± 5.709	5.110 ± 5.516	7.232	0.027	1 > 3
Five digit test cognitive flexibility	8.980 ± 8.611	7.330 ± 7.191	7.670 ± 7.680	12.860 ± 10.101	8.184	0.017	1 > 3
							2 > 3
Digit span backward	11.480 ± 9.573	13.920 ± 13.061	10.960 ± 8.565	10.570 ± 7.675	0.735	0.692	–

Values are frequencies or Mean ± Standard Deviation (SD); FAB, Frontal Assessment Battery.

DISCUSSION

Sleep complaints are associated with phonemic fluency, motor programming, inhibitory control, and working memory impairment. Depression symptoms presence are also associated with motor programming and working memory performances. Depression and sleep complaints interaction would determine phonemic fluency, inhibitory control, and working memory worse cognitive performances than these two conditions alone.

We found that depression is associated with less efficiency on motor programming. According to previous studies left dorsal prefrontal cortex and the right anterior cingulate cortex are more involved when subjects paid attention to the performance of a sequence of movements in comparison to automatic performance of this same task (Jueptner et al., 1997). Automatic aspects of motor performance are associated with subcortical structures, but sequential actions tasks with prefrontal networks (Fuster, 2001). It suggests that preparation of motor responses and learning of sequences of movements differs from an automatic condition and demands more from areas associated with executive function, which could be the same regions involved in depression. Studies of motor performance in depression corroborates these findings showing that cognitive difficulties increased with complexity of the tasks (Sabbe et al., 1996) and could be affected by pharmacological treatment (Mergl et al., 2007).

Long-term use of hypnotics may cause poor sleep quality (Vignola et al., 2000). It is also known that the use of benzodiazepines by older adults leads to cognitive decline (Glass et al., 2005). On the present study the use of benzodiazepines is associated with sensitivity to interference impairment. This is a component of executive functions related to selective attention measured by a task of conflicting instructions. Previous studies have also found association between attention and use of benzodiazepines (Barker et al., 2004) that could be due to inductive sedation effect (Chennu and Bekinschtein, 2012). Individuals in use of benzodiazepines showed phonemic fluency scores higher than individuals that are not in use of benzodiazepines. Considering that individuals without sleep complaints present phonemic fluency scores twice as high as those with sleep complaints, this may reflect the differences between those treated and untreated sleep disorders individuals. Those individuals treated probably have an improvement on fluency performance in comparison to untreated. Individuals in use of antidepressants also show motor programming scores higher than individuals with no use of antidepressants. Probably, this may reflect the differences between those treated and untreated individuals.

Deficits in verbal fluency are common finding after sleep loss, with reports of fewer words, and perseveration of incorrect responses, on tasks of verbal fluency (Harrison and Horne, 1998). These findings were not replicated in the study of (Tucker et al., 2010), but results have suggested an association between subjective sleep complaints and decline in phonemic fluency performance. Recently, McGregor and Alper (2015) showed that adults with sleep disorders were at a higher risk for language problems than healthy sleepers. The language problems typically co-occurred with problems of attention and executive function.

TABLE 5 | Effects of depression and sleep complaints on executive functions performance.

Dependent variables-neuropsychological assessment	Parameters	Independent variables							
		Age (years)	Formal education (years)	Gender = Female	Depression	Sleep complaints	Use of benzodiaze-pines	Use of anti-depressants	Depression/Sleep complaints interaction
FAB conceptualization	exp(β)	0.981	1.053	1.228	1.311	1.699	1.384	1.052	0.672
	p-value	0.036*	0.000*	0.147	0.607	0.334	0.398	0.802	0.486
FAB phonemic fluency	exp(β)	0.997	1.032	1.137	1.812	2.095	0.808	0.966	0.434
	p-value	0.657	0.000*	0.151	0.116	0.049*	0.016*	0.785	0.034*
FAB motor programming	exp(β)	0.987	1.021	1.274	1.684	1.859	1.141	1.392	0.605
	p-value	0.130	0.040*	0.061	0.014*	0.028	0.450	0.023*	0.112
FAB sensitivity to interference	exp(β)	0.978	1.000	0.934	1.662	1.610	6.509	0.975	0.578
	p-value	0.009*	0.984	0.517	0.137	0.175	0.040*	0.804	0.134
FAB inhibitory control	exp(β)	0.964	1.017	1.377	2.796	3.240	1.093	1.754	0.250
	P-value	0.006*	0.318	0.090	0.053*	0.036*	0.888	0.062	0.021*
FAB environmental autonomy	exp(β)	1.000	1.002	0.972	0.960	1.002	1.151	1.004	1.039
	p-value	0.581	0.252	0.115	0.239	0.885	0.133	0.856	0.246
FAB total score	exp(β)	0.985	1.016	1.125	1.036	1.168	1.087	1.092	0.843
	P-value	0.000*	0.002*	0.017*	0.709	0.094	0.290	0.125	0.136
Five digit test inhibitory control	exp(β)	1.033	0.963	0.727	0.887	1.026	0.666	0.970	0.950
	p-value	0.169	0.170	0.320	0.824	0.969	0.479	0.924	0.943
Five digit test cognitive flexibility	exp(β)	1.035	0.969	1.009	0.725	0.900	1.037	0.718	0.878
	p-value	0.009*	0.118	0.963	0.285	0.733	0.883	0.105	0.736
Digit span backward	exp(β)	0.994	1.061	1.025	3.467	3.438	1.071	0.991	0.299
	p-value	0.607	0.000*	0.873	0.000*	0.000*	0.771	0.959	0.001*

exp(β), exponentiated values of the coefficients; FAB, Frontal Assessment Battery.
**p-value < 0.05.*

The phonemic fluency is considered a complex task related to cognitive flexibility, sustained attention, inhibitory control, and semantic memory (Shao et al., 2014). All these processes for which sleep complaints determined lower scores are cognitive abilities controlled and can be considered executive functions, especially working memory and inhibitory control. Controlled processes as attention and working memory are linked to the functioning of frontal lobes (Alhola and Polo-Kantola, 2007). Whereas, the frontal areas are vulnerable to sleep disorders (Harrison et al., 2000), this can be associated with impairment in inhibitory control, working memory, and verbal fluency in individuals with sleep complaints. Another related issue is the developmental process of the executive functions. The functional apex of executive functions is reached during adulthood and from this point is expected to decline (Goh et al., 2013). The course of development these abilities are therefore associated with a curve in the inverted U shape, so such impairments are expected on older adults.

This sample was composed by low formal education older adults due to the characteristics of the origin country. Educational level is associated with cognitive decline (Ardila et al., 2000) and is considered a main factor throughout cognitive aging. Performance on FAB is influenced by formal education (Beato et al., 2012; de Paula et al., 2013a) age. In our sample formal education is associated with motor programming, FAB total scores increases, working memory, categorization, and phonemic verbal fluency. In young old percentile for illiterates is significantly different from university graduates (de Paula et al., 2013a). The scale validation study for this population (Beato et al., 2012) suggest four formal education tracks, with 50th percentile varying significantly according to the formal educational level.

The differences between age groups in performance on the FAB subtests are in agreement with previous studies which indicate a decline in executive functions over the years (Salthouse et al., 2003) even on healthy aging. Previous studies also found no age-related deficits specific to selective attention or task-switching location (Verhaeghen and Cerella, 2002). At each year added on age, conceptualization task scores decreases 1.9%, sensitivity to interference scores decreases 2.2%, inhibitory control scores decreases 3.6%, FAB total scores decreases 1.5%, and cognitive flexibility task errors increases 3.5%.

Finally, the study should be viewed in the light of these limitations: The pharmacological treatments as with antidepressants have not been completely controlled; convenience sample with inherent problems of selection. Outpatient clinic samples tend to present higher prevalence of cardiovascular diseases and other conditions increased by aging compared to the general population. Some confounders like these vascular risk factors or diseases were not controlled. The sleep evaluation of was not performed by a sleep specialist and the sleep quality evaluation depends on self report. It is known that depressed patients tend to overestimate or underestimate their sleep problems in self reports; The use of FAB to evaluate executive functions is also limited due to being a screening test and because items are evaluated on a scale between 0 and 3 points, which reduces the variation range. Additionally, Outpatient clinic samples tend to present higher prevalence of cardiovascular diseases and other conditions increased by aging compared to the general population. Some confounders like these vascular risk factors or diseases were not controlled.

Our findings suggest that depression and sleep are associated with impairment on executive functions in non-demented older adults, and that use of benzodiazepines and educational level are important variables. These data are important because executive functions are predictors of dementia in older adults.

AUTHOR CONTRIBUTIONS

All authors contributed and participated in the preparation of the article and all research steps: KMA contributed to the study on conception and design, on the statistical analysis, interpretation of data, wrote this article and approved the final version of the manuscript; MC contributed with acquisition of data, on supervising the geriatric assessment of the participants, on the statistical analysis, manuscript writing, and approved the final version of the manuscript; LM helped to design the study, on supervising the geriatric assessment of the participants, reviewed the statistical analysis and the manuscript and approved the final version of the manuscript; BD contributed to the study on conception and design, reviewed the statistical analysis and the manuscript, and approved the final version of the manuscript.

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REFERENCES

Alhola, P., and Polo-Kantola, P. (2007). Sleep deprivation: impact on cognitive performance. *Neuropsychiatr. Dis. Treat.* 3, 553.

Ardila, A., Ostrosky-Solis, F., Rosselli, M., and Gómez, C. (2000). Age-related cognitive decline during normal aging: the complex effect of education. *Arch. Clin. Neuropsychol.* 15, 495–513. doi: 10.1016/S0887-6177(99)00040-2

Barker, M. J., Greenwood, K. M., Jackson, M., and Crowe, S. F. (2004). Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Arch. Clin. Neuropsychol.* 19, 437–454. doi: 10.1016/S0887-6177(03)00096-9

Bastien, C. H., Fortier-Brochu, É., Rioux, I., LeBlanc, M., Daley, M., and Morin, C. M. (2003). Cognitive performance and sleep quality in the elderly suffering from chronic insomnia: relationship between objective and subjective

measures. *J. Psychosom. Res.* 54, 39–49. doi: 10.1016/S0022-3999(02)00544-5

Beato, R., Amaral-Carvalho, V., Guimarγes, H. C., Tumas, V., Souza, C. P., Oliveira, G. N. D., et al. (2012). Frontal assessment battery in a Brazilian sample of healthy controls: normative data. *Arq. Neuropsiquiatr.* 70, 278–280. doi: 10.1590/S0004-282X2012005000009

Benca, R. M., and Peterson, M. J. (2008). Insomnia and depression. *Sleep Med.* 9, S3–S9. doi: 10.1016/S1389-9457(08)70010-8

Cajochen, C., Knoblauch, V., Kräuchi, K., Renz, C., and Wirz-Justice, A. (2001). Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure. *Neuroreport* 12, 2277–2281. doi: 10.1097/00001756-200107200-00046

Chennu, S., and Bekinschtein, T. A. (2012). Arousal modulates auditory attention and awareness: insights from sleep, sedation, and disorders of consciousness. *Front. Psychol.* 5:65. doi: 10.3389/fpsyg.2012.00065

de Paula, J. J., Bertola, L., Ávila, R. T., Moreira, L., Coutinho, G., de Moraes, E. N., et al. (2013a). Clinical applicability and cutoff values for an unstructured neuropsychological assessment protocol for older adults with low formal education. *PLoS ONE* 8:e73167. doi: 10.1371/journal.pone.0073167

de Paula, J. J., Moura, S. M., Bocardi, M. B., Moraes, E. N., Malloy-Diniz, L. F., and Haase, V. G. (2013b). Screening for executive dysfunction with the Frontal Assessment Battery: psychometric properties analysis and representative normative data for Brazilian older adults. *Psicol. Pes.* 7, 89–98. doi: 10.5327/Z1982-1247201300010010

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., and Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br. J. Psychiatry* 202, 329–335. doi: 10.1192/bjp.bp.112.118307

Elderkin-Thompson, V., Kumar, A., Mintz, J., Boone, K., Bahng, E., and Lavretsky, H. (2004). Executive dysfunction and visuospatial ability among depressed elders in a community setting. *Arch. Clin. Neuropsychol.* 19, 597–611. doi: 10.1016/j.acn.2003.08.009

Fuster, J. M. (2001). The prefrontal cortex—an update: time is of the essence. *Neuron* 30, 319–333. doi: 10.1016/S0896-6273(01)00285-9

Glass, J., Lanctôt, K. L., Herrmann, N., Sproule, B. A., and Busto, U. E. (2005). Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 331:1169. doi: 10.1136/bmj.38623.768588.47

Goh, J. O., Beason-Held, L. L., An, Y., Kraut, M. A., and Resnick, S. M. (2013). Frontal function and executive processing in older adults: process and region specific age-related longitudinal functional changes. *Neuroimage* 69, 43–50. doi: 10.1016/j.neuroimage.2012.12.026

Hahn, E. A., Wang, H. X., Andel, R., and Fratiglioni, L. (2014). A change in sleep pattern may predict Alzheimer disease. *Am. J. Geriatr. Psychiatry* 22, 1262–1271. doi: 10.1016/j.jagp.2013.04.015

Haimov, I., Hanuka, E., and Horowitz, Y. (2008). Chronic insomnia and cognitive functioning among older adults. *Behav. Sleep Med.* 6, 32–54. doi: 10.1080/15402000701796080

Harrison, Y., and Horne, J. (1998). Sleep loss impairs short and novel language tasks having a prefrontal focus. *J. Sleep Res.* 7, 95–100. doi: 10.1046/j.1365-2869.1998.00104.x

Harrison, Y., Horne, J. A., and Rothwell, A. (2000). Prefrontal neuropsychological effects of sleep deprivation in young adults–a model for healthy aging? *Sleep* 23, 1067–1073.

Jueptner, M., Stephan, K. M., Frith, C. D., Brooks, D. J., Frackowiak, R. S. J., and Passingham, R. E. (1997). Anatomy of motor learning. I. Frontal cortex and attention to action. *J. Neurophysiol.* 77, 1313–1324.

Jungwirth, S., Zehetmayer, S., Hinterberger, M., Kudrnovsky-Moser, S., Weissgram, S., Tragl, K. H., et al. (2011). The influence of depression on processing speed and executive function in nondemented subjects aged 75. *J. Int. Neuropsychol. Soc.* 17, 822–831. doi: 10.1017/S135561771100083X

Kraemer, S., Danker-Hopfe, H., Dorn, H., Schmidt, A., Ehlert, I., and Herrmann, W. M. (2000). Time-of-day variations of indicators of attention: performance, physiologic parameters, and self-assessment of sleepiness. *Biol. Psychiatry.* 48, 1069–1080. doi: 10.1016/S0006-3223(00)00908-2

Lim, J., and Dinges, D. F. (2010). A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136, 375. doi: 10.1037/a0018883

McCullagh, P., and Nelder, J. A. (1983). *Generalized Linear Models*. New York, NY; London: Chapman and Hall.

McGregor, K. K., and Alper, R. M. (2015). Sleep disorders as a risk to language learning and use. *EBP Briefs* 10, 1–21.

Mergl, R., Pogarell, O., Juckel, G., Rihl, J., Henkel, V., Frodl, T., et al. (2007). Hand-motor dysfunction in depression: characteristics and pharmacological effects. *Clin. EEG Neurosci.* 38, 82–88. doi: 10.1177/155005940703800210

Nebes, R. D., Butters, M. A., Mulsant, B. H., Pollock, B. G., Zmuda, M. D., Houck, P. R., et al. (2000). Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychol. Med.* 30, 679–691. doi: 10.1017/S0033291799001968

Nebes, R. D., Buysse, D. J., Halligan, E. M., Houck, P. R., and Monk, T. H. (2009). Self-reported sleep quality predicts poor cognitive performance in healthy older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 64, 180–187. doi: 10.1093/geronb/gbn037

Sabbe, B., Hulstijn, W., Van Hoof, J., and Zitman, F. (1996). Fine motor retardation and depression. *J. Psychiatr. Res.* 30, 295–306. doi: 10.1016/0022-3956(96)00014-3

Salthouse, T. A., Atkinson, T. M., and Berish, D. E. (2003). Executive functioning as a potential mediator of age-related cognitive decline in normal adults. *J. Exp. Psychol. Gen.* 132:566. doi: 10.1037/0096-3445.132.4.566

Schmidt, C., Collette, F., Cajochen, C., and Peigneux, P. (2007). A time to think: circadian rhythms in human cognition. *Cogn. Neuropsychol.* 24, 755–789. doi: 10.1080/02643290701754158

Shao, Z., Janse, E., Visser, K., and Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Front. Psychol.* 5:772. doi: 10.3389/fpsyg.2014.00772

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol. Bull.* 139, 81–132. doi: 10.1037/a0028727

Tucker, A. M., Whitney, P., Belenky, G., Hinson, J. M., and Van Dongen, H. P. (2010). Effects of sleep deprivation on dissociated components of executive functioning. *Sleep* 33, 47–57.

Verhaeghen, P., and Cerella, J. (2002). Aging, executive control, and attention: a review of meta-analyses. *Neurosci. Biobehav. Rev.* 26, 849–857. doi: 10.1016/S0149-7634(02)00071-4

Vignola, A., Lamoureux, C., Bastien, C. H., and Morin, C. M. (2000). Effects of chronic insomnia and use of benzodiazepines on daytime performance in older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 55, P54–P62.

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Psychological Disorders and Ecological Factors Affect the Development of Executive Functions: Some Perspectives

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The links between deficits in executive functions (EFs) (e.g., mental flexibility, inhibition capacities, etc.) and some psychological disorders (e.g., anxiety and depressive disorders) have been investigated in the past decades or so. Observations evidenced that some deficits in working memory, planning, and mental flexibility were highly correlated with anxiety and depressive disorders. The majority of studies focused on adults' population, whereas it seems important to adopt a developmental perspective to fully understand the dynamic relation of these EF/psychological disorders. We suggest to focus on the following two axes in future research: (i) relations between EF and anxiety traits through development and (ii) the possible role of external factors such as parent–child relationships on the development of EF.

Keywords: psychological disorders, development, parenting, executive functions, children

INTRODUCTION

One possible short definition of executive functions (EFs) is that they are adaptive, goal-directed behaviors that enable individuals to override more automatic responses (1, 2). EFs reflect a cognitive function that incorporates a set of abilities, which aims to coordinate and control processes such as planning skills. From a developmental perspective, EFs play an important role in the development of learning and in socio-cognitive abilities (3, 4). Although the study of EF in adulthood has long been a field of active research, little is known about early EF development. One of the reasons for this gap is the lack of age-appropriate EF tasks. Nonetheless, some studies evidenced that the first 5 years of life play a critical role in the development of EF (5, 6). Early work on infants and primates suggests that the prefrontal cortex (PFC) is operative since birth in humans and in other species (7–11). In fact, children are born with the potential to develop these skills. Despite growing interest in the development of EF, it is not clear whether this development is associated with psychological factors and/or external ones. Indeed, some clinical studies evidenced that EF deficits can be impaired by specific psychological factors such as anxiety depression and stress in adults (12, 13), whereas other studies evidenced that ecological factors such as socioeconomic status (SES) could impact EF.

In the present paper, we propose to explore the possible links between the development of EF, psychological disorders, and ecological factors based on the following two axes: (i) the links between EF and psychological factors such as anxiety disorders and (ii) the possible role

of ecological factors such as macro- and micro-environmental characteristics on the development of EF.

RELATIONS BETWEEN EXECUTIVE FUNCTIONS AND ANXIETY DISORDERS

In this section, we present how psychological disorders such as anxiety can affect the development of EF in adults and adolescents. The links between EF and anxiety are more and more explored since the last decades or so (14–17). Nonetheless, the relations between EF and anxiety from a developmental perspective are far from being established and clear. Still, we do not know much about the developmental trajectory of this link and the factors that could play a role.

Deficits in some aspects of EF such as attention and memory are frequently reported in studies on anxiety disorders in adults. The main anxiety disorders explored in these studies are obsessive–compulsive disorder (OCD), posttraumatic stress disorder (PTSD), social anxiety disorder (SAD), generalized anxiety disorder (GAD), and panic disorder at a given age (children, teenagers, or adults).

Goussé et al. (18) found that adults with OCD symptoms have specific deficits in spatial working memory and planning. Memory, attention, and processing speed are also impaired in these adult populations (19). The dysfunction of EF, attention, verbal, and visual memory has been reported as being associated with PTSD in adults (20). Olff et al. (21) also indicate that PTSD patients have poorer flexibility and set shifting, planning, and working memory than trauma-exposed controls. Other studies have also shown deficits in EF in patients with SAD, such as poorer cognitive flexibility (22, 23). There are also links between panic disorders and deficits in EF in adults (24).

These relations between anxiety disorders and deficits in EF in adults can be in part explained by external factors. Indeed, stressful life events can cause temporary changes in PFC functioning, which negatively affects EF and results in impaired ability for cognitive inhibition (25).

Interestingly, the relations between anxiety disorders and EF impairment are present earlier than adulthood, but results are mixed. For example, teenagers (i.e., a non-clinical population), who present anxiety symptoms such as GAD, have been reported with deficits in EF in some studies (26). A study by Yang et al. (27) showed that children and adolescents with PTSD related to a natural disaster have deficits only in the emotional control domain compared with controls exposed to the same disaster. Other studies evidenced no links between GAD and EF in clinical adults' samples (14, 28). How can we explain those mixed results? One way would be to take a developmental perspective. For example, children with OCD symptoms showed deficits in mental set shifting supporting the frontal–striatal dysfunction hypothesis of OCD diagnosis in children as well as in adults (29). Van den Heuvel et al.'s (30) study supports the hypothesis that decreased dorsal prefrontal–striatal responsiveness is associated with impaired planning capacity in OCD patients. Because the described frontal–striatal dysfunction in OCD is independent of state anxiety and disease symptom severity, they concluded that executive impairment is a core feature in OCD.

Other studies exist but they considered a broader range of disorders called "internalizing problems" that encompass anxiety disorders and depression. Riggs et al. (31) conducted a prospective study with 6- to 9-year-old children in regular classrooms over a period of 2 years. They found that proficient inhibitory control and sequencing ability were predictive of reduction of internalizing problems. Besides, some studies with children and adolescents with internalizing disorders have evidenced impaired performance on several aspects of the EF especially linked to anxiety profiles (29, 32, 33). For example, children with OCD have impaired perceptual organization ability under time pressure compared to a control population.

Longitudinal studies are needed to explore the developmental aspect of EF, but their existence is very sparse so far. Indeed, such studies demand a very large data collection with large samples and a lot of time for delayed results. Besides, in this particular area, the lack of developmental studies may be also explained by two factors: (1) late interest in studying the link between EF and psychological disorders through development trajectories (4) and (2) differences of conceptual models of anxiety disorders that are not easily understandable from a neuropsychological perspective (17). Until now the psychological models of anxiety have only been less integrated to neuroscience research (17, 34–36). Theoretical progress is necessary to fill the gap between neurobiological data, self-assessment, and clinical data. Sharp et al. (17) suggested the creation of transdiagnostics anxiety constructs that are particularly useful to connect the psychophysiological data and the psychological models of anxiety. More precisely, some studies evidenced both heightened right-lateralized activity and left-lateralized activity across a wide range of DSM anxiety disorders such as GAD, panic disorder, SAD, and OCD (37, 38). It is an important point as authors (17) suggest to disentangle between the anxious apprehension and the anxious arousal during the examination of anxiety with regard to other constructs such as EF to avoid confusion (39).

THE POSSIBLE ROLE OF ECOLOGICAL FACTORS ON THE DEVELOPMENT OF EF

Based on Bronfenbrenner's ecological systems theory (40), it might be hypothesized that some external factors could play a role in the development of EF. This hypothesis identifies some environmental factors with which an individual interacts, such as the macrosystem that refers to the cultural contexts, or SES in which individuals live, and the microsystem that describes the groups that directly influence the child's development (e.g., family members and language). Thus, in this section, we review possible links between the development of EF and some macro- and micro-environmental factors. Given its physiological characteristics such as longer maturation, the PFC is especially sensitive to ecological factors (41, 42). Therefore, EFs are thought to develop as a result of a dynamic interaction between the child's PFC and the external environment (43, 44). The link between characteristics of the child's environment, as well as the quality of

parent–child relationships, and child's cognitive development has received growing interest in the past decades or so (45).

Ecological influences may be conceptualized at different levels including the macro-environments (i.e., cultural context, for example, SES), and the micro-environments (i.e., the family setting and parent–child relationships) (46, 47). Thus, microenvironmental factors such as parents "scaffolding" (48) means that a child reach higher levels of comprehension and skill acquisition, thanks to adults' support. At the beginning, they are dependent on adult support, and then they become more independent of the way they acquire new knowledge. Thus, this support could help children to improve their executive function skills (learning to coordinate and control processes) before they must perform by their own. It is important for children to develop these skills through social relations. Indeed, social partners will teach them to cope with stress, to face issues, and to provide opportunities for directing their own actions (decision making) without any adult's control. It was shown that adverse environments resulting from neglect, abuse, violence, stress, and SES of the family may expose children to toxic stress, which disrupts brain architecture and impairs and seriously delays the development of EF (49, 50). Also, stress, lack of sleep, loneliness, or lack of exercise each could impair EF (51).

Macro-Environmental Factors and the Development of EF

An important macro-environmental factor that seems to play a role on the development of EF is the characteristics of the family setting such as SES. Some studies demonstrated that family SES is associated with children's working memory and cognitive control (52–55). More recently, Sarsour et al. (56) studied the independent and interactive associations between family SES and single parenthood to predict child EF. Single parent and family SES were associated with children' inhibitory control and cognitive flexibility such that children from low SES families who were living with one parent performed less well on EF tests than children from similarly low SES who were living with two parents. Interestingly, this study demonstrates interactions between different external factors and children EF. Moreover, mediation models help us to better understand the interaction between macro-environmental and the development of EF: the links between SES and EF are at least partially explained by associated variations in parenting behaviors (57). Besides, the level of stress, associated with a negative affectivity, has also been pointed out for its mediation role between macro-environmental factors and the development of EF (58).

Micro-Environmental Factors and the Development of EF

The Case of Bilingualism

An important aspect in the child's micro-environment is the language used at home and more specifically the fact that children may grow up in a mono- or bi-lingual environment. Some studies evidenced enhanced abilities of bilingual children to coordinate the executive control components required in performing complex tasks (59, 60). This link appears to be present early in the development as an advantage for bilingual 7- to 12-month-old infants on inhibitory control and attention over monolingual infants of the same age has been evidenced (61, 62). Therefore, it seems that executive control develops earlier in bilingual children than in comparable monolinguals (63, 64). This advantage continues to be present later in the development as bilingual adults still outperform monolinguals on EF tasks (65–67). Therefore, the mastery of two languages provides bilingual speakers cognitive benefits over monolinguals, particularly on cognitive flexibility and selective attention. To the best of our knowledge, only one study explored the effect of the bilingualism factor on EF longitudinally showing a task-specific advantage in inhibitory control in bilingual toddlers (68). Another micro-environmental factor that influences the development of EF is the role of parenting.

The Role of Parenting

Vygotsky (69) accounted that the interaction with a more competent social partner, such as the parent, fosters children's higher order cognitive functions. From this socio-constructivist point of view, the development of EF can be considered as a transfer from inter- to intra-personal regulation. The link between quality of parent–infant interactions and subsequent child's EF has been explored only recently.

Three dimensions of parenting have been associated with the development of EF (70): scaffolding, sensitivity, and mind-mindedness. Most of the studies have focused on scaffolding. This large concept refers to how parental guidance enables children to achieve level of problem solving, which they could not have reached on their own. Hughes and Ensor (71) showed that maternal scaffolding was more predictable of the development of EF at 2–4 years than imitation model or than more global positive or negative models. In another study, Bernier et al. (72) explored the relationship between scaffolding (measured as autonomy support), sensitivity, and mind-mindedness on the one hand and conflict EF[1] and impulse control on the other hand. Parenting habits were observed during free play and problem solving sessions at 12, 18, and 23 months and were correlated with several measures of EF at 18 and 26 months in 80 mother–child dyads. Independent of maternal education and general cognitive ability, they found that (1) sensitivity at 12 months was predictive of the development of conflict EF at 26 months; (2) mind-mindedness at 12 months was predictive of working memory at 18 months and of increase in EF skills between 18 and 23 months; and (3) scaffolding at 12 months was predictive of working memory and categorization at 18 months and conflict EF at 26 months. In another study, Bernier et al. (73) investigated the link between maternal interactive behavior, paternal interactive behavior, and child attachment security between 1 and 2 years of age, and child EF at 2 and 3 years. The results suggest that parental behavior and child attachment are related to child performance on EF tasks especially on cognitive flexibility components. These findings suggest that parent–child relationships may play an important

[1]Factors including measures of working memory, set shifting, and inhibition control.

role in children's developing self-regulatory capacities. More recently, Bernier et al. (74) confirmed this predictive role of attachment security at 2 years on the development of EF at 5–6 years.

The following two explanations can be made: (1) parenting provides the child with the social context in which to practice emerging regulatory skills and (2) parenting may affect brain structures involved in EF, especially the response to stress system, as it has been demonstrated in studies with animals (75). Indeed, Wagner et al. (76) evidenced that children with poorer EF had higher levels of salivary cortisol (i.e., related to stress level), and their parents reported higher parenting stress. Hence it seems that parenting and other psychological factors such as stress are important to understand the development of EF.

CONCLUSION

The idea of the present review was to explore the relations between EF and factors such as anxiety disorders and parenting through development. Much of the early influences on later EF dysfunctions appear to be transmitted through the quality of parent–child interaction during early childhood (57) and may also depend on the development of frontal brain areas and the stress response system. Interestingly, the studies reporting relationships between parenting practice and the development of EF have pointed out impacts only on some specific aspects of EF, namely, working memory and cognitive flexibility (71–73, 77). Possible hypothesis can be proposed to explain the link between EF, anxiety, and some ecological factors: (1) parenting is the main factor that impact EF development; (2) SES and bilingual environments are two important side factors playing a role in the development of EF as they are related to parental practices; and (3) poorer parenting behaviors together with a poor environment could impact EF development and predict anxiety symptoms. Interestingly, these possible scenarios are linked together. Future studies should explore the neural and social mechanisms underlying the links between parent–child relationships and the development of EF. Here, we also highlight the links between some anxiety disorders and deficits in EF. Future clinical research should take into account the transdiagnosic anxiety construct (17). It is possible that different levels of anxiety apprehension and anxiety arousal could explain results observed in previous research on the link between anxiety and EF. If these two dimensions are taken into account in a transdiagnosis construct, we could precise which dimension is associated with which aspect of EF independent of the DSM diagnosis. Investigating this axis of research would also help clarifying the pathogenesis of diverse forms of anxiety and the potential deficits in EF through development. In that sense, it would be interesting to explore the multifactorial dimensions (i.e., internal and external factors: anxiety and parent–child relationships) on the development of EF. Innovative tools, providing the support for children to develop these EF skills at home, in early care units, and in education programs, will offer new perspectives to explore the influence of children environment, parenting behavior, and clinical profiles on early development of EF. Furthermore, if we have to take into account the developmental timetable, ecological and external factors, and the variability of the clinical symptomatology, new studies should investigate the development of EF from a longitudinal perspective with infants' population and the impact of this factors on EF (cognitive) development. These new directions of research could also help to promote clinical and neuropsychological tests and to set up remediation tools for very young children.

AUTHOR CONTRIBUTIONS

All the authors participated to writing of the paper. RZ and BG contributed equally to the writing.

REFERENCES

1. Lezak MD. *Neuropsychological Assessment*. 3rd ed. New York: Oxford University Press (1995).
2. Mesulam MM. The human frontal lobes: transcending the default mode through contingent encoding. In: Stuss DT, Knight RT, editors. *Principles of Frontal Lobe Function*. Oxford: Oxford University Press (2002). p. 8–30.
3. Lyon GR, Krasnegor NG, McMenamin S. Attention, memory, and executive function. *J Dev Behav Pediatr* (1996) 17(4):278. doi:10.1097/00004703-199608000-00014
4. Roy A, Le Gall D, Roulin JL, Fournet N. Les fonctions exécutives chez l'enfant: approche épistémologique et sémiologie clinique. *Rev Neuropsychol* (2013) 4(4):287–97. doi:10.3917/rne.044.0287
5. Welsh MC, Pennington BF. Assessing frontal lobe functioning in children: views from developmental psychology. *Dev Neuropsychol* (1988) 4:199–230. doi:10.1080/87565648809540405
6. Welsh MC, Pennington BF, Groisser DB. A normative-developmental study of executive function. *Dev Neuropsychol* (1991) 7:131–49. doi:10.1080/87565649109540483
7. Diamond A. Development of the ability to use recall to guide action, as indicated by infants' performance on AB. *Child Dev* (1985) 56:868–83. doi:10.2307/1130099
8. Diamond A. Developmental time course in human infants and infant monkeys, and the neural bases of inhibitory control in reaching. *Ann N Y Acad Sci* (1990) 608:637–76. doi:10.1111/j.1749-6632.1990.tb48913.x
9. Diamond A. The development and neural bases of memory functions as indexed by the AB and delayed response tasks in human infants and infant monkeys. *Ann N Y Acad Sci* (1990) 608:267–317. doi:10.1111/j.1749-6632.1990.tb48900.x
10. Diamond A, Goldman-Rakic PS. Evidence for involvement of prefrontal cortex in cognitive changes during the first year of life: comparison of performance of human infant and rhesus monkeys on a detour task with transparent barrier. *Neuroscience* (1985) 11:832.
11. Diamond A, Goldman-Rakic PS. Comparison of human infants and rhesus monkeys on Piaget's AB task: evidence for dependence on dorsolateral prefrontal cortex. *Exp Brain Res* (1989) 74:24–40. doi:10.1007/BF00248277
12. Moritz S, Birkner C, Kloss M, Jahn H, Hand I, Haasen C, et al. Executive functioning in obsessive-compulsive disorder, unipolar depression, and schizophrenia. *Arch Clin Neuropsychol* (2002) 17:477–83. doi:10.1093/arclin/17.5.477
13. Han G, Helm J, Lucha C, Zahn-Waxler C, Hastings PD, Klimes-Dougan B. Are executive functioning deficits concurrently and predictively associated with depressive and anxiety symptoms in adolescents? *J Clin Child Adolesc Psychol* (2016) 45(1):44–58. doi:10.1080/15374416.2015.1041592
14. Airaksinen E, Larsson M, Forsell Y. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *J Psychiatr Res* (2005) 39:207–14. doi:10.1016/j.jpsychires.2004.06.001
15. Barrett LF. The conceptual act theory: a précis. *Emot Rev* (2014) 6(4):292–7. doi:10.1177/1754073914534479

16. Eysenck MW, Derakshan N, Santos R, Calvo MG. Anxiety and cognitive performance: attentional control theory. *Emotion* (2007) 7:336–53. doi:10.1037/1528-3542.7.2.336
17. Sharp PB, Miller GA, Heller W. Transdiagnostic dimensions of anxiety: neural mechanisms, executive functions, and new directions. *Int J Psychophysiol* (2015) 98(2):365–77. doi:10.1016/j.ijpsycho.2015.07.001
18. Goussé V, Delorme R, Chabane N, Perez-Diaz F, Flavie M, Mouren-Siméoni MC, et al. Fonctions exécutives dans le trouble obsessionnel compulsif: effet de l'âge de début des troubles. *Lencéphale* (2005) 31(6):666–71. doi:10.1016/S0013-7006(05)82424-8
19. Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lönnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *J Affect Disord* (2008) 106(1):1–27. doi:10.1016/j.jad.2007.06.006
20. Ferreri F, Lapp LK, Peretti CS. Current research on cognitive aspects of anxiety disorders. *Curr Opin Psychiatry* (2011) 24(1):49–54. doi:10.1097/YCO.0b013e32833f5585
21. Olff M, Polak AR, Witteveen AB, Denys D. Executive function in posttraumatic stress disorder (PTSD) and the influence of comorbid depression. *Neurobiol Learn Mem* (2014) 112:114–21. doi:10.1016/j.nlm.2014.01.003
22. Fujii Y, Kitagawa N, Shimizu Y, Mitsui N, Toyomaki A, Hashimoto N, et al. Severity of generalized social anxiety disorder correlates with low executive functioning. *Neurosci Lett* (2013) 543:42–6. doi:10.1016/j.neulet.2013.02.059
23. Frick A, Howner K, Fischer H, Eskildsen SF, Kristiansson M, Furmark T. Cortical thickness alterations in social anxiety disorder. *Neurosci Lett* (2013) 536:52–5. doi:10.1016/j.neulet.2012.12.060
24. Hovland A, Pallesen S, Hammar Å, Hansen AL, Thayer JF, Tarvainen MP, et al. The relationships among heart rate variability, executive functions, and clinical variables in patients with panic disorder. *Int J Psychophysiol* (2012) 86(3):269–75. doi:10.1016/j.ijpsycho.2012.10.004
25. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *Ann Behav Med* (2009) 37(2):141–53. doi:10.1007/s12160-009-9101-z
26. Tempesta D, Mazza M, Serroni N, Moschetta FS, Di Giannantonio M, Ferrara M, et al. Neuropsychological functioning in young subjects with generalized anxiety disorder with and without pharmacotherapy. *Prog Neuropsychopharmacol Biol Psychiatry* (2013) 45:236–41. doi:10.1016/j.pnpbp.2013.06.006
27. Yang R, Xiang YT, Shuai L, Qian Y, Lai KY, Ungvari GS, et al. Executive function in children and adolescents with posttraumatic stress disorder 4 and 12 months after the Sichuan earthquake in China. *J Child Psychol Psychiatry* (2014) 55(1):31–8. doi:10.1111/jcpp.12089
28. Smitherman TA, Huerkamp JK, Miller BI, Houle TT, O'Jile JR. The relation of depression and anxiety to measures of executive functioning in a mixed psychiatric sample. *Arch Clin Neuropsychol* (2007) 22:647–54. doi:10.1016/j.acn.2007.04.007
29. Shin MS, Choi H, Kim H, Hwang JW, Kim BN, Cho SC. A study of neuropsychological deficit in children with obsessive-compulsive disorder. *Eur Psychiatry* (2008) 23(7):512–20. doi:10.1016/j.eurpsy.2008.03.010
30. Van den Heuvel OA, Veltman DJ, Groenewegen HJ, Witter MP, Merkelbach J, Cath DC, et al. Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Arch Gen Psychiatry* (2005) 62(8):922–33. doi:10.1001/archpsyc.62.8.922
31. Riggs NR, Blair CB, Greenberg MT. Concurrent and 2-year longitudinal relations between executive function and the behavior of 1st and 2nd grade children. *Child Neuropsychol* (2004) 9(4):267–76. doi:10.1076/chin.9.4.267.23513
32. Beers SR, De Bellis MD. Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. *Am J Psychiatry* (2002) 159(3):483–6. doi:10.1176/appi.ajp.159.3.483
33. Toren P, Sadeh M, Wolmer L, Eldar S, Koren S, Weizman R, et al. Neurocognitive correlates of anxiety disorders in children: a preliminary report. *J Anxiety Disord* (2000) 14(3):239–47. doi:10.1016/S0887-6185(99)00036-5
34. Lang PJ. Fear reduction and fear behavior: problems in treating a construct. In: Schlien J, editor. *Research in Psychotherapy III*. Washington, DC: APA (1968). p. 90–103.
35. Lang PJ. Anxiety: toward a psychophysiological definition. In: Akiskal HS, Webb WL, editors. *Psychiatric Diagnosis: Exploration of Biological Predictors*. New York: Spectrum (1978). p. 365–89.
36. Kozak MJ, Miller GA. Hypothetical constructs versus intervening variables: a reappraisal of the three-systems model of anxiety assessment. *Behav Assess* (1982) 14:347–58.
37. Heller W, Nitschke JB. The puzzle of regional brain activity in depression and anxiety: the importance of subtypes and comorbidity. *Cogn Emot* (1998) 12:421–47. doi:10.1080/026999398379664
38. Nitschke JB, Heller W, Miller GA. Anxiety, stress, and cortical brain function. In: Borod JC, editor. *The Neuropsychology of Emotion*. New York, NY: Oxford University Press (2000). p. 298–319.
39. Moser JS, Moran TP, Schroder HS, Donnellan MB, Yeung N. On the relationship between anxiety and error monitoring: a meta-analysis and conceptual framework. *Front Hum Neurosci* (2013) 7:466. doi:10.3389/fnhum.2013.00466
40. Bronfenbrenner U. Ecological systems theory. In: Vasta R, editor. *Annals of Child Development. Six Theories of Child Development: Revised Formulations and Current Issues*. London: Jessica Kingsley Publishers (1992). p. 187–249.
41. Diamond A. Normal development of prefrontal cortex from birth to young adulthood: cognitive functions, anatomy, and biochemistry. In: Stuss DT, Knight RT, editors. *Principles of Frontal Lobe Function*. London: Oxford University Press (2002). p. 466–503.
42. Diamond A. The early development of executive functions. In: Bialystock E, Craik FIM, editors. *Lifespan Cognition: Mechanisms of Change*. Oxford, England: Oxford University Press (2006). p. 70–95.
43. Calkins SD, Fox NA. Self-regulatory processes in early personality development: a multilevel approach to the study of childhood social withdrawal and aggression. *Dev Psychopathol* (2002) 14:477–98. doi:10.1017/S095457940200305X
44. Diamond A. All or none hypothesis: a global-default mode that characterizes the brain and mind. *Dev Psychol* (2009) 45:130–8. doi:10.1037/a0014025
45. Garon N, Bryson SE, Smith IM. Executive function in preschoolers: a review using an integrative framework. *Psychol Bull* (2008) 134:31–60. doi:10.1037/0033-2909.134.1.31
46. Baumeister RF, Vohs KD. Sexual economics: sex as female resource for social exchange in heterosexual interactions. *Pers Soc Psychol Rev* (2004) 8:339–63. doi:10.1207/s15327957pspr0804_2
47. Hertzman C, Boyce T. How experience gets under the skin to create gradients in developmental health. *Annu Rev Public Health* (2010) 31:329–47. doi:10.1146/annurev.publhealth.012809.103538
48. Vygotski LS. *Myslenie i rec'. French translation: Pensée et langage*. In: Sève F, editor. Paris: Messidor/Éditions Sociales (1934).
49. McClelland MM, Tominey SL. The development of self-regulation and executive function in young children. *Zero to Three J* (2014) 35:2–8.
50. Starcke K, Wiesen C, Trotzke P, Brand M. Effects of acute laboratory stress on executive functions. *Front Psychol* (2016) 7:461. doi:10.3389/fpsyg.2016.00461
51. Diamond A. Executive functions. *Annu Rev Psychol* (2013) 64:135–68. doi:10.1146/annurev-psych-113011-143750
52. Farah MJ, Shera DM, Savage JH, Betancourt L, Giannetta JM, Brodsky NL, et al. Childhood poverty: specific associations with neurocognitive development. *Brain Res* (2006) 1110:166–74. doi:10.1016/j.brainres.2006.06.072
53. Noble KG, Farah MJ, McCandliss BM. Socio-economic background modulates cognition-achievement relationships in reading. *Cogn Dev* (2006) 21(3):349–68. doi:10.1016/j.cogdev.2006.01.007
54. Noble KG, McCandliss BD, Farah MJ. Socioeconomic gradients predict individual differences in neurocognitive abilities. *Dev Sci* (2007) 10:464–80. doi:10.1111/j.1467-7687.2007.00600.x
55. Noble KG, Norman MF, Farah MJ. Neurocognitive correlates of socioeconomic status in kindergarten children. *Dev Sci* (2005) 8:74–87. doi:10.1111/j.1467-7687.2005.00394.x
56. Sarsour K, Sheridan M, Jutte D, Nuru-Jeter A, Hinshaw S, Boyce WT. Family socioeconomic status and child executive functions: the roles of language, home environment, and single parenthood. *J Int Neuropsychol Soc* (2011) 17:120–32. doi:10.1017/S1355617710001335
57. Rhoades BL, Greenberg MT, Lanza ST, Blair C. Demographic and familial predictors of early executive function development: contribution of a person-centered perspective. *J Exp Child Psychol* (2011) 108(3):638–62. doi:10.1016/j.jecp.2010.08.004

58. He Z-H, Yin W-G. Family environments and children's executive function: the mediating role of children's affective state and stress. *J Genet Psychol* (2016) 177(5):143–55. doi:10.1080/00221325.2016.1218322
59. Bialystok E. Coordination of executive functions in monolingual and bilingual children. *J Exp Child Psychol* (2011) 110:461–8. doi:10.1016/j.jecp.2011.05.005
60. Morales J, Yudes C, Gómez-Ariza CJ, Bajo MT. Bilingualism modulates dual mechanisms of cognitive control: evidence from ERPs. *Neuropsychologia* (2015) 66:157–69. doi:10.1016/j.neuropsychologia.2014.11.014
61. Kovács AM, Mehler J. Cognitive gains in 7-month-old bilingual infants. *Proc Natl Acad Sci U S A* (2009) 106:6556–60.
62. Kovács ÁM, Mehler J. Flexible learning of multiple speech structures in bilingual infants. *Science* (2009) 5940:611–2. doi:10.1126/science.1173947
63. Adi-Japha E, Berberich-Artzi J, Libnawi A. Cognitive flexibility in drawings of bilingual children. *Child Dev* (2010) 81(5):1356–66. doi:10.1111/j.1467-8624.2010.01477.x
64. Bialystok E. Global-local and trail-making tasks by monolingual and bilingual children: beyond inhibition. *Dev Psychol* (2010) 46:93–105. doi:10.1037/a0015466
65. Bialystok E, Craik FI, Klein R, Viswanathan M. Bilingualism, aging, and cognitive control: evidence from the Simon task. *Psychol Aging* (2004) 19(2):290. doi:10.1037/0882-7974.19.2.290
66. Costa A, Hernández M, Sebastián-Gallés N. Bilingualism aids conflict resolution: evidence from the ANT task. *Cognition* (2008) 106:59–86. doi:10.1016/j.cognition.2006.12.013
67. Prior A, MacWhinney B. A bilingual advantage in task switching. *Biling Lang Cognit* (2010) 13:253–62. doi:10.1017/S1366728909990526
68. Cristina Crivello C, Kuzyk O, Rodrigues M, Friend M, Zesiger P, Poulin-Dubois D. The effects of bilingual growth on toddlers' executive function. *J Exp Child Psychol* (2016) 141:121–32. doi:10.1016/j.jecp.2015.08.004
69. Vygotsky L. Interaction between learning and development. In: Gauvain M, Cole M, editors. *Readings on the Development of Children*. New York: Scientific (1978). p. 34–41.
70. Carlson SM. Executive function in context: development, measurement, theory, and experience. *Monogr Soc Res Child Dev* (2003) 68(3):138–51. doi:10.1111/j.1540-5834.2003.06803012.x
71. Hughes CH, Ensor RA. How do families help or hinder the emergence of early executive function? *New Dir Child Adolesc Dev* (2009) 123:35–50. doi:10.1002/cd.234
72. Bernier A, Carlson SM, Whipple N. From external regulation to self-regulation: early parenting precursors of young children's executive functioning. *Child Dev* (2010) 81(1):326–39. doi:10.1111/j.1467-8624.2009.01397.x
73. Bernier A, Carlson SM, Deschênes M, Matte-Gagné C. Social factors in the development of early executive functioning: a closer look at the caregiving environment. *Dev Sci* (2012) 15(1):12–24. doi:10.1111/j.1467-7687.2011.01093
74. Bernier A, Beauchamp MH, Carlson SM, Lalonde G. A secure base from which to regulate: attachment security in toddlerhood as a predictor of executive functioning at school entry. *Dev Psychol* (2015) 51(9):1177–89. doi:10.1037/dev0000032
75. Gunnar MR, Fisher PA. The early experience, stress, and prevention network. Bringing basic research on early experience and stress neurobiology to bear on preventative interventions for neglected and maltreated children. *Dev Psychopathol* (2006) 18:651–77. doi:10.1017/S0954579406060330
76. Wagner S, Müller C, Helmreich I, Huss M, Tadić A. A meta-analysis of cognitive functions in children and adolescents with major depressive disorder. *Eur Child Adolesc Psychiatry* (2015) 24:5–19. doi:10.1007/s00787-014-0559-2
77. Bibok MB, Carpendale JIM, Müller U. Parental scaffolding and the development of executive function. *New Dir Child Adolesc Dev* (2009) 123:17–34. doi:10.1002/cd.233

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Risky Decisions in a Lottery Task Are Associated with an Increase of Cocaine Use

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Cocaine use disorder is associated with maladaptive decision-making behavior, which strongly contributes to the harmful consequences of chronic drug use. Prior research has shown that cocaine users exhibit impaired neuropsychological test performances, particularly with regard to attention, learning, and memory but also in executive functions such as decision-making and impulse control. However, to what extent cocaine users show impaired decision-making under risk without feedback has not yet been investigated systematically. Therefore, to examine risk-taking behavior, 31 chronic cocaine users and 26 stimulant-naïve healthy controls who were part of the Zurich Cocaine Cognition Study, performed the Randomized Lottery Task (RALT) with winning lotteries consisting of an uncertain and a certain prospect. Results revealed that risky decisions were associated with male sex, increased cocaine use in the past year, higher cocaine concentrations in the hair, and younger age. In addition, higher levels of cocaine in the hair and cumulative lifetime consumption were associated with risky decisions, whereas potentially confounding factors including cognition and psychiatric symptoms had no significant effect. Taken together, our results indicate that cocaine users who increased their consumption over a period of 1 year show deficits in the processing of risky information accompanied with increased risk-taking. Future research should analyse whether risky decisions could potentially serve as a prognostic marker for cocaine use disorder.

Keywords: stimulants, impulsivity, gambling, addiction, risky choices, economics, reward, drug dependence

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INTRODUCTION

Did cocaine use cause the financial crisis? David Nutt has been heavily criticized for his provocative statement that cocaine-using bankers with their "culture of excitement and drive and more and more and more... got us into this terrible mess" (Anderson, 2013). However, when mechanisms for dealing with uncertain information fail, as in psychiatric conditions such as cocaine use disorder, the results can really be disastrous for the individual (Bolla et al., 1998; Zack and Poulos, 2009) and result in high economic and societal costs (Olesen et al., 2012). Cocaine is the second most

used illegal drug in Europe after cannabis (EMCDDA, 2014) and is considered to be the second most harmful drug after heroin (Nutt et al., 2007). Apparently, about 5–6% of cocaine users get addicted within the first year after first use, while 15–16% develop dependency in the long term (Wagner and Anthony, 2002). However, there is yet a lack of longitudinal data and, thus, it remains unclear why some individuals get addicted and others evade an addiction. Although, cocaine is an unselective monoamine reuptake inhibitor (Iversen et al., 2013), its acute rewarding effects have been primarily linked to the inhibition of dopamine transporter function and consequently, increased dopamine levels in the synaptic cleft (Ritz et al., 1987). There is mounting evidence that chronic cocaine consumption is associated with persistent structural and functional adaptive changes in brain areas involved in motivation, reward, judgment, and inhibitory control of behavior (Robinson and Kolb, 2004; Koob and Volkow, 2010). Neuropsychiatric manifestations of cocaine use disorder involve decrements in cognitive domains of attention, working memory, declarative memory, social cognition, and executive functions including decision-making and impulse control (Jovanovski et al., 2005; Nnadi et al., 2005; Verdejo-Garcia et al., 2007; Vonmoos et al., 2013a,b; Hulka et al., 2014; Preller et al., 2014). Specifically, the maladaptive decision-making strategies of cocaine users have been considered to be both: (i) similar to deficits observed in patients with lesions in the orbitofrontal and ventromedial prefrontal cortex; and (ii) an essential attribute of addictive behavior (Bechara, 2005). As effective pharmacological treatment options are currently lacking (Quednow and Herdener, 2016), an adequate characterization of maladaptive decision making as a potential core feature of cocaine addiction could be useful for the development of effective prevention and treatment strategies.

Hence, the effect of chronic drug use on decisions that involve uncertainty, or incomplete knowledge about how choices lead to outcomes, is an important field of addiction research. Indeed, in daily life we continually face trade-offs between options that promise safety and others that carry both potential for jackpot and threat. Sometimes we receive immediate feedback and are able to learn fast and, therefore, improve our decision behavior, whereas other times the outcomes of our decisions are delayed and we only learn slowly over time. In behavioral economics, uncertainty occurs in two domains with different ranges of incompleteness of information: *risk* refers to situations where the expected value of the outcomes are known (e.g., lotteries, insurance); whereas *ambiguity* indicates their likelihood is unknown and is often simply referred to as *uncertainty* (Platt and Huettel, 2008; Shafir, 2008).

Interestingly, most studies on the effect of cocaine use on decision behavior have so far focused on *ambiguous information with feedback*. They have provided evidence that chronic cocaine use is linked to deficits in the processing of reward and punishment contingencies, as measured by the Iowa Gambling Task (IGT; Bechara and Damasio, 2002; Verdejo-Garcia et al., 2007; Kjome et al., 2010). Consequently, it has been suggested that dependent cocaine users fail to incorporate ongoing feedback to guide future behaviors and instead, make impulsive decisions that are based on immediate reward availability (Bechara et al., 2002).

In this study we focussed on decisions under *risky information without feedback* in cocaine users in comparison to an age-, sex-, and verbal intelligence-matched healthy control group. Risky decisions without immediate feedback allow a derivation of solid parameters for the expected value of the outcomes, in contrast to tasks with ambiguous information, such as the IGT. We used a general linear model (GLM) approach enabling a multivariate means of establishing the predictive value of demographic (e.g., sex, age, cognitive function), task-related (e.g., probability), and cocaine- (e.g., dose) related variables concerning risky decisions. Based on a prior study demonstrating deficits in cocaine users in risky decision-making with feedback (Gorini et al., 2014), we hypothesized that cocaine users are more prone to risky decisions and that elevated risk-taking is associated with increased cocaine use.

METHODS

Participants

All individuals were tested in the 1-year follow-up measurement of the Zurich Cocaine Cognition Study (ZuCo2St; Vonmoos et al., 2013a; Hulka et al., 2014; Vonmoos et al., 2014; Hulka et al., 2015). The recruitment of participants took place at drug prevention and treatment centers, psychiatric hospitals, through advertising in local newspapers, internet platforms, and by word-of-mouth communication (for details see Vonmoos et al., 2013a). Inclusion criteria for all participants were: (1) age between 18 and 60 years, (2) proficiency in German language, (3) no use of prescription drugs affecting the CNS, (4) no current or previous Axis I DSM-IV psychiatric disorder (in cocaine users with exception of cocaine abuse/dependence and/or alcohol and nicotine abuse/dependence, attention deficit hyperactivity disorder, and a history of depression), (5) no neurological disorder or head injury, and (6) no family history of a severe DSM-IV psychiatric disorder such as schizophrenia, bipolar disorder, or obsessive-compulsive disorder. Cocaine users had to meet the DSM-IV criteria for either cocaine abuse or dependence to be included in the study.

Prior to the follow up measurements, participants were instructed to abstain from illegal drugs for $\geq$3 days and from alcohol $\geq$24 h. Additionally healthy controls were excluded if they regularly engaged in illegal drug use (>15 occasions) with the exception of occasional cannabis use. Hair samples (6 cm) from all participants were collected at baseline and follow-up and subsequently analyzed with liquid chromatography-mass spectrometry to exclude participants with opioid use and/or pronounced poly-toxic drug use patterns and to objectively characterize cocaine use over the past 6 months (for details see Vonmoos et al., 2013a). In the hair, the concentrations (pg/mg) of cocaine and its main metabolites benzoylecgonine and norcocaine were determined. The total cocaine (coc_{tot}) concentration in the hair was then calculated by the following formula according to Hoelzle et al. (2008): coc_{tot} = cocaine + benzoylecgonine + norcocaine. Additionally, the concentration of cocaethylene (coc_{eth}) was measured. Coc_{eth} is an ethyl ester of

benzoylecgonine formed by the human liver metabolism when cocaine and ethanol co-occur in the blood. Thus, coc_{eth} is a reliable marker for the concomitant use of cocaine and ethanol (Pennings et al., 2002).

Of the 132 participants (79 cocaine users, 53 stimulant-naïve controls) participating in the ZuCo^{2}St follow-up, 27 (22 cocaine users, 5 controls) were excluded from the analyses, either because of illegal drug use detected in the hair and not allowed by our exclusion criteria (e.g., opioids or excessive MDMA intake), or because of newly initiated treatment with psychotropic medication (e.g., methylphenidate, antipsychotics, or antidepressants). The risk task was administered in 60 participants (34 cocaine users and 26 controls) only at the follow-up measurement. As one cocaine user had to be excluded from the analysis due to random decision-making and two cocaine users were excluded due to illegal drug use other than cocaine (see above), the final sample consisted of 31 cocaine users and 26 controls. Cocaine users were further divided into groups of (i) 10 persons with a strong increase of cocaine hair concentrations between baseline and 1-year follow-up (*increasers*), (ii) 12 persons with a strong decrease of cocaine hair concentrations (*decreasers*), and (iii) 9 users with largely unchanged cocaine use between both measurement time points (*equal users*). Criteria for increasing and decreasing cocaine use were determined by a combination of absolute and relative changes of cocaine concentration in hair samples between baseline and follow-up. The absolute criterion was based on a shift in cocaine hair concentration of at least 500 pg/mg, according to a commonly accepted cut-off value for reliable detection of cocaine use (Bush, 2008; Cooper et al., 2012). The relative criterion was based on a minimal increase of 20% or a minimal decrease of 10% in coc_{tot} (Vonmoos et al., 2014; Hulka et al., 2015).

The Ethics Committee of the Canton of Zurich approved the study. All participants provided written, informed consent and were compensated for their participation.

Clinical Interviews and Questionnaires

At the follow-up, all participants were interviewed with the Structured Clinical Interview for DSM-IV Disorders (SCID-I), which was carried out by a trained psychologist (APA, 1994). Drug use patterns were assessed by means of the Interview for Psychotropic Drug Consumption (IPDC), which has been described in detail elsewhere (Quednow et al., 2004). The brief version of the Cocaine Craving Questionnaire (CCQ) was used to assess current cocaine craving in cocaine users (Sussner et al., 2006). Current symptoms of depression were measured with the Beck Depression Inventory (BDI; Beck et al., 1961). Attention Deficit Hyperactivity Disorder (ADHD) symptoms were assessed with the ADHD Self-Rating Scale (ADHD-SR; Roesler et al., 2004).

Neuropsychological Tests

Participants underwent a broad neuropsychological and social cognitive test battery as well as psychophysiological measurements, which have been described in detail elsewhere (Preller et al., 2013, 2014; Vonmoos et al., 2013a; Hulka et al., 2014). In order to control for the influence of attention, working memory and long-term memory, four representative tests were included into the statistical model as confounding factors: The Letter Number Sequencing Task (LNST) was used to measure verbal working memory function (Wechsler, 1997), for which the dependent variable was the number of correct answers. The Spatial Working Memory task (SWM) strategy score from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Strauss et al., 2006) was used to measure spatial working memory and executive function. The number of total errors tested the capability to retain spatial information and to manipulate remembered items. The Rapid Visual Processing task (RVP) from the CANTAB was administered to assess sustained attention (dependent variable: A′, a signal detection measure of sensitivity that incorporates how well a person is able to detect target sequences). The German version of the Rey Auditory Verbal Learning Test (RAVLT) was administered to assess the verbal declarative memory performance (Helmstaedter et al., 2001), for which the dependent variables were learning performance (Σ trials 1–5) and delayed recall (trial 7).

Risk Task

One of the most common methods to elicit risky decisions without feedback in experimental economics involves the use of binary choice tasks that present winning lotteries in "multiple price lists" (Charness et al., 2013). Participants are presented with a set of binary lotteries where they choose from two options: (A) a lottery with an expected value; and (B) a guaranteed payoff, i.e., a cash amount that can be earned with certainty (Tversky, 1992; Schubert and Brown, 1999; Fehr-Duda, 2006). One multiple price list depicts several decisions with a fixed winning probability and decreasing guaranteed payoff, and therefore when filled out depicts the decision-maker's transition from the safe to the uncertain alternative, or their "indifference point." Anderson et al. (2007) reported three disadvantages for multiple price lists: First, they are based on internal responses only. Second, subjects often switch back and forth between the choice alternatives, resulting in inconsistent preference elicitation. Third, the multiple price list approach could be susceptible to framing effects, because subjects have a tendency to start in the middle of the table irrespective of the presented values. These disadvantages can be overcome with an experimental task with automatic data capturing that offers the single, binary lotteries in a randomized order. Here we describe such an experimental task, which simulates ecologically valid decisions under risky information with no direct feedback.

At the 1-year- follow-up, all participants performed an interactive risk task, the Randomized Lottery Task (RALT). The task presented a set of 20 binary lotteries to each subject on a computer screen, with each lottery consisting of: option A) a lottery with an expected value characterized by a randomized winning probability of 50 CHF; and option B) a guaranteed payoff that was randomly distributed between zero and the maximum outcome (50 CHF). For example, participants decided between 50 CHF with a probability of 25% *or* a guaranteed payoff of 25 CHF. Different lotteries were automatically generated for each trial: the winning probability and therefore the expected value of the lotteries as well as the guaranteed payoff were fully

randomized and equally distributed in the interval between zero and one, in order to allow a comparison between trials and to avoid artifacts.

The RALT started by informing each participant that he/she will play the task for real money. Participants were informed that after completing the RALT, one of the lotteries would be randomly chosen and paid out in real money. A sequence of 20 lotteries appeared on the screen and participants had to make a choice for each of them regarding option A or B. The series of choices was recorded as a sequence consisting of 0 (guaranteed payoff rejected) and 1 (guaranteed payoff preferred) representing the choice behavior (*C*) in our analysis. As the task does not give any feedback, players cannot adapt their strategies over time and the monetary payoff is only revealed at the very end of the game. Therefore, each player acts independently on each decision, which is a prerequisite for the statistical analysis applied. The task additionally recorded the lotteries' so-called uncertainty premium (*up*), which is defined as the difference between the expected value of the lottery minus the value of the guaranteed payoff. Under rationality assumptions, a negative *up* of the lottery would lead to "risk-prone" behavior, whereas a positive *up* would lead to "risk-averse" behavior. The sequence of lotteries was randomized and data were recorded automatically and without immediate feedback. Both the user interface and the data-capture procedure were implemented with Visual Basic for Application (VBA) and a spreadsheet program (Microsoft EXCEL 2007).

Definition of Variables

Following Montgomery (1999), we defined four types of variables (**Table 1**), namely the response variable, covariates, factors, and nuisance covariates: risk behavior *C*, captured by the RALT, was our response variable that we aimed to explain with covariates (cocaine consumption, lotteries *up*, and age parameters; measured continuously on a scale), which are modified by factors (sex, cocaine user group, and cocaine craving; discrete classes) and nuisance variables (ADHD symptoms, depressive symptoms, attention, verbal, and spatial working memory, as well as verbal declarative memory). Prior findings have provided compelling evidence that dependent (Jovanovski et al., 2005; Vonmoos et al., 2013a) and to some extent also recreational cocaine users (Soar et al., 2012; Vonmoos et al., 2013a) exhibit broad neurocognitive deficits in attention, verbal, and spatial working memory, as well as verbal declarative memory. Moreover, cocaine users are more likely to suffer from depression and ADHD (Vonmoos et al., 2013a). Therefore, in order to control for potentially confounding effects of these nuisance variables on risk-taking behavior, we included them in the GLM. **Table 1** provides additional description and the acquisition method.

Statistical Analysis

The statistical analysis was based on generalized linear models (McCullagh and Nelder, 1989) using the statistical software R, aiming to identify a model that best explains the choice behavior (C) with the explanatory variables (**Table 1**). Since the response variable is binary, a logit transformation was used, assuming linearity of all the explanatory variables in the logit space (Equation 1):

$$g(n) = \mu + up + p + SEX_i + [COC_{it} + ...] + [CCQ + BZT + RAVLT_{sum}] + \varepsilon_{ij} \quad (1)$$

where η, linear predictor; $g()$, link function [logit]; μ, overall mean; *up*, lotteries uncertainty premium [CHF, risk task input]; *p*, probability of the uncertain alternative; SEX_j, sex [factor, i = m, f]; [coc_{lt}+…], cocaine use parameters [see **Table 1**]; [CCQ,…], nuisance due to craving and cognitive detriment [see **Table 1**]; ε_{ij}, error term, binomial distributed.

Linear and generalized linear models assume a lack of multicollinearity in the explanatory variables, which was analyzed with correlation diagnostics (R *cor* function). The model consists of three classes of explanatory variables: (1) the utility parameters (mean value μ, *up*, sex), (2) cocaine use parameters (estimated lifetime cocaine use [coc_{lt}], CCQ score, hair parameters coc_{eth} and coc_{tot},), and (3) cognitive and clinical covariates (ADHD, BDI, RVP, LNST, $RAVLT_{sum}$, $RAVLT_7$, SWM). As the number of observations in each class of sex (male, female) was unbalanced, which is typical for observational studies, a weighted squares of means analysis (Searle, 1987) was necessary.

A log transformation of the cocaine use parameters (coc_{lt}, coc_{eth}, coc_{tot}, CCQ) was calculated in order to eliminate the heavy skewness of the data distribution and increase the homogeneity of the residual variance. To identify the subset of variables with the highest explanatory power the following strategy was used: first, in order to depict the power of single effects, a type II deviance analysis was calculated, which is an analog to the variance analysis in linear models (Fox et al., 2011). A type II analysis compares the full model with all variables with (full-1) models that sequentially leave-one-out of all variables (Langsrud, 2003). Strategies for developing models and for the selection of the variables also recommend investigating the effect of first-order interactions (e.g., sex***up*). Second, an applied standard procedure was used to estimate the values and standard errors of parameters (**Tables 5, 6**), including backwards stepwise elimination based on the Akaike Information Criterion (R *stepAIC function*). Since this procedure may risk over-fitting models, we used variance inflation metrics (R *vif function*) to estimate the severity of multicollinearity and eliminate collinear explanatory variables. Third, we performed model diagnostics, such as studentized residuals, hat values and cook's distance to assess if error distributions were homogeneous and if there were influential or leveraging observations (R *influencePlot*). The outlier analysis was performed with the R *outlierTest* function.

As a risk measure derived from the choice behavior *C*, we calculated the indifference points, where the probabilities of choosing options A or B were both 0.5. This approach has been used widely in experimental economics. We calculated indifference points for all groups (*increasers, decreasers, equal users, control)* based on cocaine toxicological hair analyses (**Figure 1**). For each of the indifference points, confidence intervals were estimated in logit space and transformed back

TABLE 1 | Definition of variables and acquisition methods.

Variable type	Symbol	Description of variable	Acquisition method
Response	*C*	Binary variable 0 choice of the uncertain alternative 1 choice of the safe alternative	Automatically recorded by the RALT
Covariates	*up*	Uncertainty premium of the safe alternative of a lottery Expected value (x; p)–cash value (y; 1)	Automatically recorded by the RALT
	p	Probability of the uncertain alternative of a lottery	Automatically recorded by the RALT
	coc_{lt}	Lifetime amount of cocaine (g)	Drug interview
	coc_{eth}	Cocaethylene in the hair (pg/mg)	LC-MS/MS analysis of the hair
	coc_{tot}	Sum of cocaine, and its metabolites benzoylecgonine and norcocaine in the hair (pg/mg)	LC-MS/MS analysis of the hair
	age	Biological age (y)	Questionnaire
Factor	SEX	Biological aspects of femaleness/maleness	Questionnaire
	INC	Cocaine concentration measured in hair Factor 10 controls (no cocaine use) 20 increasing cocaine use 30 decreasing cocaine use 40 steady cocaine use	LC-MS/MS analysis of the hair
	CCQ	Craving for cocaine (score 0–70)	Cocaine Craving Questionnaire
Nuisance covariates	ADHD	Attention deficit hyperactivity disorder symptoms (score 0–54)	ADHD Questionnaire
	BDI	Symptoms of depression (score 0–63)	Beck Depression Inventory
	RVP	Sustained attention (score 0–1)	Rapid Visual Processing task CANTAB
	LNST	Verbal working memory (score 0–24)	Letter Number Sequencing Task
	RAVLTsum	Verbal declarative memory performance (Σtrials 1–5, score 0–75)	Rey Auditory Verbal Learning Test
	RAVLT7	Verbal declarative memory, delayed recall (score 0–15)	Rey Auditory Verbal Learning Test
	SWM	Spatial Working Memory/Executive function (score 1–37)	Spatial Working Memory task CANTAB

LC-MS/MS, liquid chromatography-tandem mass spectrometry.

to the observation space. As the indifference points depend on the *up* of the lotteries, they were depicted as a probability distribution, our additional risk metric (**Figure 2**).

RESULTS

Demographic Variables and Drug Use

Table 2 presents means, standard deviations and *t*-test statistics for demographic variables and drug use patterns. Healthy controls and cocaine users did not differ with regard to age and verbal IQ. In contrast, cocaine users had significantly fewer years of education and higher depression and ADHD scores compared to healthy controls. There was also a trend toward a greater number of males in the cocaine users than in the control group. Cocaine users had an average lifetime cocaine consumption of 744 g and hair toxicology analyses confirmed that cocaine was the primary drug of choice.

Neuropsychological Tests and Risk Task

In order to control for general neuropsychological performance with regard to preferences in the RALT risk task, verbal working memory function (LNST), spatial working memory and executive function (SWM), sustained attention (RVP'A), and verbal declarative memory performance were measured (RAVLT; **Table 2**). Healthy controls and cocaine users did not significantly differ with regard to the RVP A′, LNST, and SWM, but cocaine users performed significantly worse in both RAVLT parameters, reflecting impaired verbal declarative learning capacity and reduced delayed verbal recall. With regard to the RALT, cocaine users had significantly higher *C* values, indicating that cocaine users on average preferred the risky alternative.

Task Correlations

The correlation-matrix identifies collinearities within a data set, which is a prerequisite for proper GLM-model selection. **Table 3** depicts the correlation coefficients. In order to avoid accumulation of alpha error, the significance threshold for correlations was set at $p < 0.01$. Decision behavior *C* was significantly correlated with the *up* of the lotteries ($r = 0.46$). Moreover, coc_{lt} was negatively correlated with sustained attention (RVP), working memory (LNST), verbal learning capacity (RAVLT_sum), and verbal long-term memory (RAVLT7). Additionally, increased coc_{eth} in hair was correlated with reduced sustained attention, suggesting that the pronounced concomitant use of alcohol and cocaine is considerably worse for cognitive functioning, as shown previously (Bolla et al., 2000). These findings recapitulate the previously-reported correlations between cocaine use and cognitive impairment in this sample (Vonmoos et al., 2013a, 2014). Finally, higher age was correlated

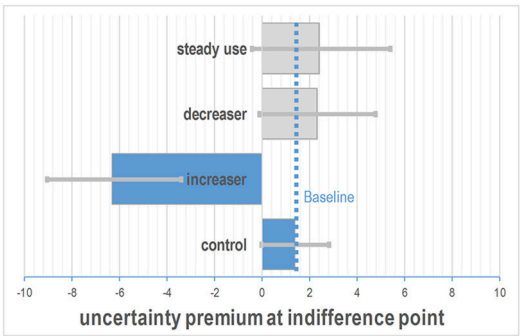

FIGURE 1 | Difference in indifference points between the controls and the groups of cocaine users. Increasers had negative indifference points indicating increased risk-taking behavior. The dotted line depicts the indifference point of the control group as the baseline condition. The estimated uncertainty premium was calculated for the four increaser classes with SEX = female; age = 30, $p = 0.5$. Bars depict estimated 95% confidence intervals.

with lower verbal working memory, while several additional cognitive parameters were intercorrelated (e.g., worse sustained attention was associated with decreased verbal declarative memory and an increased, i.e., less efficient, SWM strategy score).

The three parameters (coc_{lt}, coc_{eth}, coc_{tot}) were heavy-tailed: about 90% of the coc_{eth}, coc_{tot} data are located in the lowest 10% of the data range, whereas this amount is close to 75% for coc_{lt}. Therefore, a log-transformation of these parameters was used in further calculations to eliminate the heavy skewness of the data distribution and increase the homogeneity of the residual variance.

Analysis of Deviance

The analysis of variance likelihood ratio test of the RALT parameter *C* including all 15 explanatory variables was significant for seven variables (**Table 4**). Explanatory variables with a stronger effect on risk-taking *C* had a higher likelihood ratio, measured with the likelihood chi-square. Concerning first-order interactions, the interaction of *up* and sex was chosen in the final model, as the partial deviance of this interaction term is higher than the sum of partial deviance of the two single variables.

The interaction of the lotteries *up* and sex had the strongest effect, followed by the lotteries winning probability, increase in cocaine use, the cocaine concentration in the hair and age. A model with 15 parameters bears the risk of over-fitting and variance inflation. The variance inflation test yielded five variables with a variance inflation factor higher than 5, which indicated the presence of collinearities that were omitted in the next step.

Model Based on Changing Cocaine Use Patterns within 1 Year

The stepwise selection procedure based on the Akaike Information Criterion (AIC) resulted in a model with 5 parameters only (**Table 5**): the interaction of the lotteries *up* and sex, the lotteries winning probability, cocaine use pattern and age. Since cocaine use pattern is a factor with 4 levels, a single parameter was estimated for each level, whereas the standard level equals the intercept. Only users with an increase of cocaine use (level 20) were significantly different from the controls (level 10).

TABLE 2 | Demographic data, drug use patterns, neuropsychological and risk tasks.

	Stimulant-naïve controls ($n = 26$)	Cocaine users ($n = 31$)	*t*	*df*	*p*
DEMOGRAPHY					
Age	31.62 (9.14)	30.81 (7.87)	0.36	55	0.72
Sex (number/%)	10/16 38/62%	5/26 16/84%	3.64‡	1	0.06
Verbal IQ	109.58 (11.64)	106.32 (9.28)	1.18	55	0.25
Years of education	11.10 (1.80)	10.16 (1.49)	2.11	55	**0.04**
BDI	1.85 (2.33)	8.35 (9.50)	–3.69	55	**0.00**
ADHD-SR score	7.69 (4.92)	14.97 (8.88)	–3.90	55	**0.00**
COCAINE USE					
Lifetime (g)	–	744.04 (927.09)	–	–	–
Coc_{tot} (pg/mg)	–	14120 (37769)	–	–	–
Coc_{eth} (pg/mg)	–	818 (1750)	–	–	–
CCQ	–	18.06 (8.84)	–	–	–
NEUROPSYCHOLOGICAL TESTS					
RVP A′	0.94 (0.04)	0.92 (0.04)	1.78	55	0.08
LNST	15.19 (2.79)	14.61 (3.03)	0.75	55	0.46
RAVLT7	13.92 (1.73)	12.65 (2.51)	2.24	54	**0.03**
$RAVLT_{sum}$	66.56 (5.46)	60.65 (9.34)	2.96	54	**0.01**
SWM	30.00 (6.81)	32.48 (4.52)	–1.59	55	0.12
RISK TASK (RALT)					
C	0.39(0.49)	0.45(0.49)	–2.09	1123	**0.04**
up	–2.14(9.4)	–1.38(9.25)	–1.39	1106	0.16
p	0.49(0.26)	0.47(0.26)	1.16	1102	0.25

BDI, Beck Depression Inventory; ADHD-SR, Attention-Deficit Hyperactivity Disorder Self-Rating Scale; C, choice behavior; Coctot, cocaine + benzoylecgonine + norcocaine concentration in hair; Coceth, ethylcocaine in hair sample; CCQ, Cocaine Craving Questionnaire; p, probability of the uncertain alternative, RVP A′, Rapid Visual Processing task A′; LNST, Letter Number Sequencing Task; RAVLT sum, Rey Auditory Verbal Learning Test (Σtrials 1-5); RAVLT7, Rey Auditory Verbal Learning Test (trial 7); SWM, Spatial Working Memory; up, uncertainty premium. Significant p-values are shown in bold. Statistical tests: Independent t-tests for continuous data and ‡chi² for frequency data.

Figure 1 shows that the estimated indifference points of the *increasers* were negative, indicating strong risk-taking behavior, whereas controls, steady users and *decreasers* had a positive risk premium, indicating a more risk adverse behavior. The depicted indifference points correspond to the lotteries *up* with the highest probability of choice.

Figure 2 depicts the effect of the explanatory variables on the probability distribution of the indifference point, depending on the *up* of the lotteries. Increasing cocaine use and high cocaine concentrations in the hair were associated with participants' negative *up* indicating risk-prone behavior. Male sex was associated with a smaller variability in the distribution of the indifference points.

Model Based on Cocaine Hair Concentrations

The stepwise selection procedure based on AIC resulted in a 4 parameter model (**Table 6**) consisting of the interaction of the lotteries *up* and sex, the lotteries winning probability,

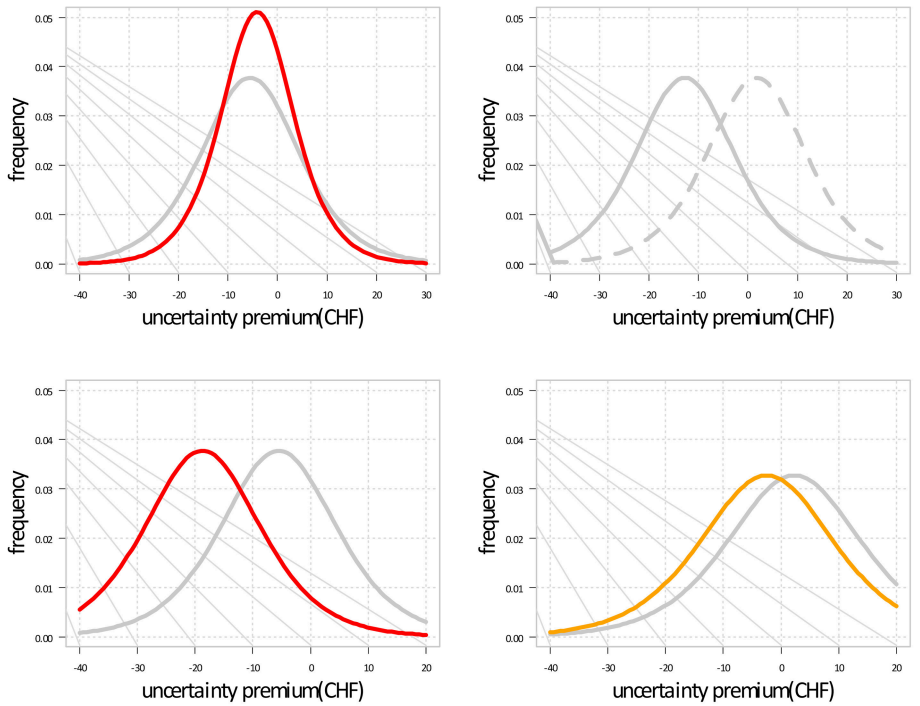

FIGURE 2 | Effect of sex, winning probability, increasing cocaine use, and cocaine in the hair on the participants' choice depicted by the distribution of the indifference points. Negative uncertainty premiums represent risk-prone behavior, while positive values indicate risk-averse behavior. [upper left] male (red) behavior shows smaller variability; [upper right] the change of the winning probability from 0.05 to 0.95 (pointed line) results in a shift toward risk-aversion; [lower left] increasing cocaine use (red) results in a shift toward risk-proneness; [lower right] high cocaine concentration in the hair (yellow) at the 95% quantile of all individuals results in a slight shift toward risk-proneness.

and the logarithm of average of coc_{tot} in the hair. Coc_{tot} was automatically selected because it showed a higher effect than cocaethylene and cumulative lifetime consumption of cocaine on risk taking. All the parameters were significant at $p < 0.001$ and the test for variance inflation resulted in values close to one, indicating no co-linearity.

Figure 2 (lower right) depicts the effect of cocaine concentrations in the hair on the probability distribution of the indifference point and indicates that high cocaine concentrations in the hair were associated with participants' negative *up*, indicating risk-prone behavior.

DISCUSSION

In this study, we report on differences in non-social decision-making without immediate feedback in cocaine users in comparison with a control group. Careful psychiatric diagnostic procedures ensured that cocaine users had few psychiatric co-morbidities and detailed toxicological hair analyses showed relatively sparse polysubstance use. Importantly, we used the GLM analysis approach as a technique to identify demographic, task-related, and cocaine-related variables with the highest explanatory power for risk-taking. Our study yielded the following major findings: (I) Cocaine users, as a group, are more prone to risky decisions in a lottery task in comparison to a matched control group without regular drug use. (II) Risky decisions are associated with male sex, self-reported increase in cocaine use, higher amounts of cocaine in the hair and younger age. More specifically, (III) *increasers* made significantly more risky decisions in the lotteries than the other groups as they chose less favorable options with a higher probability for losing in the lottery task, depicted by a negative indifference point. Moreover, (IV) higher concentrations of cocaine in the hair and cumulative lifetime consumption of cocaine across all user groups were associated with risky decisions, whereas potentially confounding factors like attention, working memory, long-term memory, symptoms of depression and ADHD had no significant effect. Taken together, our results indicate that cocaine users who increased their consumption in the last 12 months show deficits in the processing of risky information and exhibit increased risk-taking in comparison to the other groups of cocaine users and controls.

To our knowledge, the effect of cocaine use on *risky decisions without feedback* has not yet been investigated with an experimental economic analysis approach. One study examined *risky decisions with immediate feedback* in the game of dice task that presents choices between different lotteries with known expected utility. In congruence with our results, cocaine users made a significantly reduced number of safe bets although they only gambled with hypothetical monetary gains (Gorini et al., 2014).

TABLE 3 | Correlation-matrix with *r*-values for cardinal variables.

	C	*up*	*p*	coc_{lt}	coc_{eth}	coc_{tot}	Age	RVP	LNST	$RAVLT_{sum}$	$RAVLT_7$	SWM
C	1.00											
up (lot)	**0.46**	1.00										
p	−0.26	0.07	1.00									
coc_{lt}	0.01	0.04	−0.07	1.00								
coc_{eth}	−0.11	0.04	0.00	**0.40**	1.00							
coc_{tot}	−0.07	0.03	−0.02	**0.48**	**0.87**	1.00						
Age	−0.10	0.01	0.00	0.27	0.20	0.25	1.00					
RVP	0.06	−0.03	0.03	**−0.44**	**−0.40**	−0.32	−0.30	1.00				
LNST	0.02	0.04	0.04	**−0.33**	−0.21	−0.32	**−0.34**	0.33	1.00			
$RAVLT_{sum}$	0.07	0.00	0.01	**−0.42**	−0.23	−0.27	−0.18	**0.49**	**0.34**	1.00		
$RAVLT_7$	0.07	−0.01	0.03	**−0.43**	−0.24	−0.30	−0.15	**0.42**	0.31	**0.91**	1.00	
SWM	−0.02	−0.01	−0.04	0.24	0.26	0.32	0.10	**−0.43**	−0.36	−0.28	−0.18	1.00

BDI, Beck Depression Inventory; ADHD, attention-deficit hyperactivity disorder; C, choice behavior; Coctot, cocaine, benzoylecgonine, norcocaine in hair sample; Coceth, ethylcocaine in hair sample; CCQ, cocaine craving questionnaire; p, probability of the uncertain alternative, RVP A′, Rapid Visual Processing task A′; LNST, Letter Number Sequencing Task; RAVLT sum, Rey Auditory Verbal Learning Test (Σtrials 1-5); RAVLT7, Rey Auditory Verbal Learning Test (trial 7); SWM, Spatial Working Memory; up, uncertainty premium. Significant correlations (p< 0.01) are shown in bold.

TABLE 4 | Analysis of deviance table (type II analysis).

	LR Chi^2	*df*	*p*(>Chisq)
p	79.8	1	**0.01**
CCQ	0.02	1	0.89
BDI	1.22	1	0.26
ADHD	0.01	1	0.98
Age	5.46	1	**0.02**
coc_{eth}	44.33	1	**0.01**
coc_{lt}	1.70	1	0.19
coc_{tot}	14.04	1	**0.01**
INC	61.52	4	**0.01**
RVP A′	2.11	1	0.15
LNST	2.54	1	0.11
$RAVLT_{sum}$	2.85	1	0.09
RAVLT7	0.36	1	0.53
SWM	0.16	1	0.69
*up**SEX	364.31	2	**0.01**

Deviance measures the explanatory power of the model components. The interaction of SEX and risk premium had the biggest influence, followed by the probability of the lottery p, INC, coc_{eth}, and coc_{tot}. BDI, Beck Depression Inventory; ADHD, attention-deficit hyperactivity disorder; Coctot, cocaine, benzoylecgonine, norcocaine in hair sample; Coc_{eth}, ethylcocaine in hair sample; CCQ, cocaine craving questionnaire; INC, factor group, p, probability of the uncertain alternative, RVP A′, Rapid Visual Processing task A′; LNST, Letter Number Sequencing Task; RAVLT sum, Rey Auditory Verbal Learning Test (Σtrials 1–5); RAVLT7, Rey Auditory Verbal Learning Test (trial 7); SWM, Spatial Working Memory; up, uncertainty premium. Significant p-values are shown in bold.

TABLE 5 | Parameter estimation for a model based on cocaine use patterns.

	Estimate	SE	*z*-value	Significance
(Intercept)	2.51	0.36	6.87	***
p	−2.41	0.27	−8.75	***
Age	−0.05	0.01	−5.11	***
Group (increasers)	1.08	0.22	4.97	***
Group (decreasers)	−0.13	0.20	−0.65	
Group (steady use)	−0.15	0.23	−0.64	
Group (control)	−0.15	0.52	−0.29	
*up**SEXf	0.14	0.01	9.81	***
*up**SEXm	0.19	0.02	10.57	***

*p, probability of the uncertain alternative; SEXf, female sex, SEXm, male sex; up, uncertainty premium. ***p< 0.001.*

Moreover, several previous studies have shown that cocaine users exhibit disadvantageous decision-making in *ambiguous decisions with immediate feedback* that require adequate processing of reward and punishment contingencies as measured by the IGT (Bechara et al., 2002; Verdejo-Garcia et al., 2007; Vadhan et al., 2009; Kjome et al., 2010; Balconi et al., 2014) and by the Balloon Analogue Risk Task (Canavan et al., 2014): However, some studies also report no significant effect of cocaine use on performance in either the IGT (Bolla et al., 2003; Hulka et al., 2014) or the Balloon Analogue Risk Task (Gorini et al., 2014). The reasons for these inconsistent results remain unclear. It has been suggested that dependent cocaine users fail to incorporate ongoing feedback to guide future behaviors, make impulsive decisions that are based on immediate reward (Bechara et al., 2002) and fail to learn from repeated mistakes because of an insensitivity to future consequences (Bechara, 2001).

Our results indicate that risky decisions in cocaine users can also be observed without feedback, indicating an additional and more basic mechanism than the failure to learn from immediate mistakes. Zack and Poulos (2009) proposed that "…the placing of the bet, execution of the play, and anticipation of its outcome may induce a subjective state (suspense/thrill) quite apart from the outcome itself (win/lose). Thus, in gambling,

TABLE 6 | Parameter estimation for a model based on cocaine in the hair.

	Estimate	SE	*z* value	
(Intercept)	0.88	0.16	5.59	***
p	−2.36	0.27	−8.82	***
Log (coc_{tot}+1)	0.091	0.027	3.38	***
*up**SEXf	0.13	0.014	9.32	***
*up**SEXm	0.18	0.017	10.68	***

*Coc_{tot}, cocaine, benzoylecgonine, norcocaine in hair sample; p, probability of the uncertain alternative; SEXf, female sex, SEXm, male sex; up, uncertainty premium. ***p< 0.001.*

it is possible to subjectively *like* the state of *wanting*. This is not unique to gambling; it is seen in seduction or striptease, as well as in activities like hunting. In each case, the subject enjoys the state of pursuit *per se*. [. . .]. One likely subjective correlate of such pursuit is arousal." In the present study participants received no feedback on the outcome of their decisions, however, they gambled with real money as they were informed that they would receive a monetary gain at the end of the study. Our results indicate that even without the feedback of "you win!" or "you lose!" cocaine users and controls make significantly different risky decisions. Regarding possible basic mechanisms of this finding, neurophysiological studies in monkeys reveal that dopamine neurons show phasic activations related predominantly, but not exclusively, to feedback (reward and punishment), but also without feedback to risk, expectancy of reward, and the salience of the stimulus: the activations increase with reward value, probability and their multiplied product, expected value (Schultz, 2010). Dopamine has been widely implicated in reinforcement, reward, and pleasure (Schultz, 2015). In addition, Panksepp (1998) characterized dopamine as the "seeking-system" and similarly Berridge (2007) have argued that dopamine is more strongly involved in the "wanting"—i.e., the moment before and without the feedback—than in the "liking" of a result. Dopamine therefore drives the ability to recognize a stimulus as a signal for future reward and to elicit approach behavior even without direct reward. Here, we focused on this "wanting" aspect of gambling behavior in cocaine users. Interestingly, dopamine plays a similar role in pathological gambling to its role in psychostimulant addiction: chronic exposure to both gambling and psychostimulants is believed to induce profound and long lasting changes in brain function, where sensitization of dopamine pathways are considered to play a critical underlying role in the pathological effect (Robinson and Berridge, 2001). Importantly, Zack and Poulos (2009) highlighted that the signals for uncertain reward in gambling lead to dynamic changes in dopamine release, much like that induced by psychostimulant drugs. They hypothesize that these changes in dopamine release may reinforce gambling behavior regardless of its outcome. Our results may be in accordance with this hypothesis. Following this line of thought, reward-predicting stimuli may induce a pseudo-cocaine-state of "wanting" in cocaine users leading to risk-prone behavior and the ignorance of the long-term negative consequences, due to sensitization of dopamine pathways.

It has been suggested that hypothetical monetary gains might not always offer enough incentive for gambling behavior in cocaine users, therefore—in contrast to most previous studies (Bechara and Damasio, 2002; Kjome et al., 2010; Balconi et al., 2014; Canavan et al., 2014; Gorini et al., 2014)—our participants gambled with real money. However, rewards have been shown to lose some of their value when they are delayed, even though their objective reward value is the same (Ainslie, 1975). This effect might be increased in cocaine users, since they display a highly stable preference for smaller, immediate rewards compared to larger but delayed rewards (Hulka et al., 2014, 2015). However, our results indicate that the expected reward of a monetary payment at the end of the study was large enough to motivate "wanting"—behavior in cocaine users.

There are some limitations inherent to the present study. Firstly, it is impossible to substantiate whether the differences in risky decisions in cocaine users are due to a predisposition, to cocaine-induced neuroplasticity, or to an interaction of both, given that we assessed risk-taking behavior only cross-sectionally and only at the follow-up of the $ZuCo^2St$. Secondly, our results indicate that an increase in substance use is associated with a high level of risk-taking. Importantly, these results have no prognostic value so far as risk-taking was measured only at the follow-up study. Thus, it is possible that risk-taking did increase in line with cocaine use and therefore might not be valid as a prognostic marker for the development of addiction. However, this finding is interesting for future research in the context of the question of why some users get addicted while others don't, but it remains to be shown whether risk-taking could be a predictor for the development of an addiction. Thirdly, the group size was relatively modest, mainly due to our strict inclusion criteria. However, we have measured relatively pure cocaine users with very little psychiatric and no medical comorbidities, which is also an advantage. Finally, stepwise regression procedures of the kind we employed have been criticized (Henderson and Denison, 1989; Sribney, 2011). Sribney (2011) gave a helpful overview on the problems of stepwise regression analyses—e.g., in the presence of collinearity or outliers. Importantly, a GLM analysis is only a model for reality and will never depict cause/effect relationships, only possible (statistically significant) associations.

In conclusion, our results indicate that even in risky decisions without direct feedback cocaine users differ in their behavior, exhibiting risk-proneness. Interestingly, users who have increased their consumption over a period of 1 year show deficits in the processing of risky information. Considering that real world financial risks do often come with an expected value and delayed feedback this evidence strengthens the point that cocaine use could add to mismanagement and should be avoided by decision makers. Importantly, Bechara (2005) has proposed that drug users with impaired decision-making might be more vulnerable to embarking on a downward-spiraling path, because poor decision-making leads to addiction. Following this argument, future prospective studies should analyse whether neurocognitive development depicted by risky decisions could serve as a marker for addictive disorders and success of treatment.

AUTHOR CONTRIBUTIONS

AW wrote the first draft of the manuscript and contributed to the cooperation and design of the study. The risk task was designed by HH and AW. LH and MV obtained the data. The data were analyzed by HRH as well as AW and LH. AW, LH, MV, and HH were involved in the revision of the manuscript. BQ designed the study, interpreted the results, wrote and revised the manuscript, and bears responsibility for data acquisition and analyses.

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REFERENCES

Ainslie, G. (1975). Specious reward: a behavioral theory of impulsiveness and impulse control. *Psychol. Bull.* 82, 463–496. doi: 10.1037/h0076860

Anderson, G. (2013). *Did Cocaine Use by Bankers Cause the Global Financial Crisis? The Guardian [Online]*. Available online at: http://www.theguardian.com/business/shortcuts/2013/apr/15/cocaine-bankers-global-financial-crisis

Anderson, S., Harrison, G. W., Lau, M. I., and Rutstrom, E. E. (2007). Valuation using multiple price list formats. *Appl. Econ.* 39, 675–682. doi: 10.1080/00036840500462046

APA (1994). *American Psychological Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association (APA).

Balconi, M., Finocchiaro, R., and Campanella, S. (2014). Reward sensitivity, decisional bias, and metacognitive deficits in cocaine drug addiction. *J. Addict. Med.* 8, 399–406. doi: 10.1097/ADM.0000000000000065

Bechara, A. (2001). Neurobiology of decision-making: risk and reward. *Semin. Clin. Neuropsychiatry* 6, 205–216. doi: 10.1053/scnp.2001.22927

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat. Neurosci.* 8, 1458–1463. doi: 10.1038/nn1584

Bechara, A., and Damasio, H. (2002). Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia* 40, 1675–1689. doi: 10.1016/S0028-3932(02)00015-5

Bechara, A., Dolan, S., and Hindes, A. (2002). Decision-making and addiction (part II): myopia for the future or hypersensitivity to reward? *Neuropsychologia* 40, 1690–1705. doi: 10.1016/S0028-3932(02)00016-7

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., and Erbaugh, J. (1961). An inventory for measuring depression. *Arch. Gen. Psychiatry* 4, 561–571. doi: 10.1001/archpsyc.1961.01710120031004

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology (Berl).* 191, 391–431. doi: 10.1007/s00213-006-0578-x

Bolla, K. I., Cadet, J. L., and London, E. D. (1998). The neuropsychiatry of chronic cocaine abuse. *J. Neuropsychiatry Clin. Neurosci.* 10, 280–289. doi: 10.1176/jnp.10.3.280

Bolla, K. I., Eldreth, D. A., London, E. D., Kiehl, K. A., Mouratidis, M., Contoreggi, C., et al. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage* 19, 1085–1094. doi: 10.1016/S1053-8119(03)00113-7

Bolla, K. I., Funderburk, F. R., and Cadet, J. L. (2000). Differential effects of cocaine and cocaine plus alcohol on neurocognitive performance. *Neurology* 54, 2285–2292. doi: 10.1212/WNL.54.12.2285

Bush, D. M. (2008). The U.S. Mandatory guidelines for federal workplace drug testing programs: current status and future considerations. *Forensic Sci. Int.* 174, 111–119. doi: 10.1016/j.forsciint.2007.03.008

Canavan, S. V., Forselius, E. L., Bessette, A. J., and Morgan, P. T. (2014). Preliminary evidence for normalization of risk taking by modafinil in chronic cocaine users. *Addict. Behav.* 39, 1057–1061. doi: 10.1016/j.addbeh.2014.02.015

Charness, G., Uri, G., and Alex, I. (2013). Experimental methods: eliciting risk preferences. *J. Econ. Behav. Organ.* 87, 43–51. doi: 10.1016/j.jebo.2012.12.023

Cooper, G. A., Kronstrand, R., Kintz, P., and Society of Hair, T. (2012). Society of Hair Testing guidelines for drug testing in hair. *Forensic Sci. Int.* 218, 20–24. doi: 10.1016/j.forsciint.2011.10.024

EMCDDA (2014). *European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2014. Trends and developments*. Luxembourg: Publications Office of the European Union.

Fehr-Duda, H. (2006). Gender, financial risks, and probability weights. *Theory Decis.* 60, 283–313. doi: 10.1007/s11238-005-4590-0

Fox, E., Sudderth, E. B., Jordan, M. I., and Willsky, A. S. (2011). Bayesian nonparametric inference of switching dynamic linear models. *IEEE Trans. Signal Process.* 59, 1569–1585. doi: 10.1109/TSP.2010.2102756

Gorini, A., Lucchiari, C., Russell-Edu, W., and Pravettoni, G. (2014). Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. *Front. Hum. Neurosci.* 8:661. doi: 10.3389/fnhum.2014.00661

Helmstaedter, C., Lendt, M., and Lux, S. (2001). *Verbaler Lern- und Merkfähigkeitstest*. Göttingen: Beltz.

Henderson, D., and Denison, D. R. (1989). Stepwise regression in social and psychological research. *Psychol. Rep.* 64, 251–257. doi: 10.2466/pr0.1989.64.1.251

Hoelzle, C., Scheutler, F., Uhl, M., Sachs, H., and Thieme, D. (2008). Application of discriminant analysis to differentiate between incorporation of cocaine and its congeners into hair and contamination. *Forensic Sci. Int.* 176, 13–18. doi: 10.1016/j.forsciint.2007.07.020

Hulka, L. M., Eisenegger, C., Preller, K. H., Vonmoos, M., Jenni, D., Bendrick, K., et al. (2014). Altered social and non-social decision-making in recreational and dependent cocaine users. *Psychol. Med.* 44, 1015–1028. doi: 10.1017/S0033291713001839

Hulka, L. M., Vonmoos, M., Preller, K. H., Baumgartner, M. R., Seifritz, E., Gamma, A., et al. (2015). Changes in cocaine consumption are associated with fluctuations in self-reported impulsivity and gambling decision-making. *Psychol. Med.* 45, 3097–3110. doi: 10.1017/S0033291715001063

Iversen, L., Gibbons, S., Treble, R., Setola, V., Huang, X. P., and Roth, B. L. (2013). Neurochemical profiles of some novel psychoactive substances. *Eur. J. Pharmacol.* 700, 147–151. doi: 10.1016/j.ejphar.2012.12.006

Jovanovski, D., Erb, S., and Zakzanis, K. K. (2005). Neurocognitive deficits in cocaine users: a quantitative review of the evidence. *J. Clin. Exp. Neuropsychol.* 27, 189–204. doi: 10.1080/13803390490515694

Kjome, K. L., Lane, S. D., Schmitz, J. M., Green, C., Ma, L., Prasla, I., et al. (2010). Relationship between impulsivity and decision making in cocaine dependence. *Psychiatry Res.* 178, 299–304. doi: 10.1016/j.psychres.2009.11.024

Koob, G. F., and Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology* 35, 217–238. doi: 10.1038/npp.2009.110

Langsrud, Y. (2003). ANOVA for unbalanced data: use Type II instead of Type III sums of squares. *Stat. Comput.* 13, 163–167. doi: 10.1023/A:1023260610025

McCullagh, P., and Nelder, J. A. (1989). *Generalized Linear Models*, 2nd Edn. London: Chapman & Hall.

Montgomery, D. C. (1999). Experimental design for product and process design and development. *J. R. Stat. Soc. Series D* 48, 159–177. doi: 10.1111/1467-9884.00179

Nnadi, C. U., Mimiko, O. A., Mccurtis, H. L., and Cadet, L. (2005). Neuropsychiatric effects of cocaine use disorders. *J. Natl. Med. Assoc.* 97, 1504–1515.

Nutt, D., King, L. A., Saulsbury, W., and Blakemore, C. (2007). Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 369, 1047–1053. doi: 10.1016/S0140-6736(07)60464-4

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., and Jonsson, B. (2012). The economic cost of brain disorders in Europe. *Eur. J. Neurol.* 19, 155–162. doi: 10.1111/j.1468-1331.2011.03590.x

Panksepp, J. (1998). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford: Oxford University Press.

Pennings, E. J. M., Leccese, A. P., and De Wolff, F. A. (2002). Effects of concurrent use of alcohol and cocaine. *Addiction* 97, 773–783. doi: 10.1046/j.1360-0443.2002.00158.x

Platt, M. L., and Huettel, S. A. (2008). Risky business: the neuroeconomics of decision making under uncertainty. *Nat. Neurosci.* 11, 398–403. doi: 10.1038/nn2062

Preller, K. H., Hulka, L. M., Vonmoos, M., Jenni, D., Baumgartner, M. R., Seifritz, E., et al. (2014). Impaired emotional empathy and related social network deficits in cocaine users. *Addict. Biol.* 19, 452–466. doi: 10.1111/adb.12070

Preller, K. H., Ingold, N., Hulka, L. M., Vonmoos, M., Jenni, D., Baumgartner, M. R., et al. (2013). Increased sensorimotor gating in recreational and dependent cocaine users is modulated by craving and attention-deficit/hyperactivity disorder symptoms. *Biol. Psychiatry* 73, 225–234. doi: 10.1016/j.biopsych.2012.08.003

Quednow, B. B., and Herdener, M. (2016). Human pharmacology for addiction medicine: from evidence to clinical recommendations. *Prog. Brain Res.* 224, 227–250. doi: 10.1016/bs.pbr.2015.07.017

Quednow, B. B., Kuhn, K. U., Hoenig, K., Maier, W., and Wagner, M. (2004). Prepulse inhibition and habituation of acoustic startle response in male MDMA ('ecstasy') users, cannabis users, and healthy controls. *Neuropsychopharmacology* 29, 982–990. doi: 10.1038/sj.npp.1300396

Ritz, M. C., Lamb, R. J., Goldberg, S. R., and Kuhar, M. J. (1987). Cocaine receptors on dopamine transporters are related to self-administration of cocaine. *Science* 237, 1219–1223. doi: 10.1126/science.2820058

Robinson, T. E., and Berridge, K. C. (2001). Incentive-sensitization and addiction. *Addiction* 96, 103–114. doi: 10.1046/j.1360-0443.2001.9611038.x

Robinson, T. E., and Kolb, B. (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology* 47(Suppl. 1), 33–46. doi: 10.1016/j.neuropharm.2004.06.025

Roesler, M., Retz, W., Retz-Junginger, P., Thome, J., Supprian, T., Nissen, T., et al. (2004). Instrumente zur diagnostik der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) im Erwachsenenalter. *Nervenarzt* 75, 888–895. doi: 10.1007/s00115-003-1622-2

Schubert, R., and Brown, M. (1999). Financial decision-making: are women really more risk-averse? *Am. Econ. Rev.* 89, 386–391.

Schultz, W. (2010). Dopamine signals for reward value and risk: basic and recent data. *Behav. Brain Funct.* 6:24. doi: 10.1186/1744-9081-6-24

Schultz, W. (2015). Neuronal reward and decision signals: from theories to data. *Physiol. Rev.* 95, 853–951. doi: 10.1152/physrev.00023.2014

Searle, S. R. (1987). *Linear Models for Unbalanced Data*. New York, NY: John Wiley & Sons.

Shafir, E. (2008). "Desicion making," in *MIT Encyclopedia of the Cognitive Sciences*, eds R. A. Wilson and F. C. Keil (Cambridge, MA: MIT Press), 220–223.

Soar, K., Mason, C., Potton, A., and Dawkins, L. (2012). Neuropsychological effects associated with recreational cocaine use. *Psychopharmacology (Berl).* 222, 633–643. doi: 10.1007/s00213-012-2666-4

Sribney, B. (2011). *What are Some of the Problems with Stepwise Regression [Online]. StataCorp*. Available online at: http://www.stata.com/support/faqs/statistics/stepwise-regression-problems/ (Accessed March 13, 2016).

Strauss, E., Sherman, E. M. S., and Spreen, O. A. (2006). *Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. Oxford, UK: Oxford University Press.

Sussner, B. D., Smelson, D. A., Rodrigues, S., Kline, A., Losonczy, M., and Ziedonis, D. (2006). The validity and reliability of a brief measure of cocaine craving. *Drug Alcohol Depend.* 83, 233–237. doi: 10.1016/j.drugalcdep.2005.11.022

Tversky, K. (1992). Advances in prospect theory: cumulative representation of uncertainty. *J. Risk Uncertain.* 5, 297–323. doi: 10.1007/BF00122574

Vadhan, N. P., Hart, C. L., Haney, M., Van Gorp, W. G., and Foltin, R. W. (2009). Decision-making in long-term cocaine users: effects of a cash monetary contingency on Gambling task performance. *Drug Alcohol Depend.* 102, 95–101. doi: 10.1016/j.drugalcdep.2009.02.003

Verdejo-Garcia, A., Benbrookb, A., Funderburkc, F., Davidb, P., Cadetd, J. L., and Bolla, K. (2007). The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug Alcohol Depend.* 90, 2–11. doi: 10.1016/j.drugalcdep.2007.02.004

Vonmoos, M., Hulka, L. M., Preller, K. H., Jenni, D., Baumgartner, M. R., Stohler, R., et al. (2013a). Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. *Br. J. Psychiatry* 203, 35–43. doi: 10.1192/bjp.bp.112.118091

Vonmoos, M., Hulka, L. M., Preller, K. H., Jenni, D., Schulz, C., Baumgartner, M. R., et al. (2013b). Differences in self-reported and behavioral measures of impulsivity in recreational and dependent cocaine users. *Drug Alcohol Depend.* 133, 61–70. doi: 10.1016/j.drugalcdep.2013.05.032

Vonmoos, M., Hulka, L. M., Preller, K. H., Minder, F., Baumgartner, M. R., and Quednow, B. B. (2014). Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. *Neuropsychopharmacology* 39, 2200–2210. doi: 10.1038/npp.2014.71

Wagner, F. A., and Anthony, J. C. (2002). From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 26, 479–488. doi: 10.1016/S0893-133X(01)00367-0

Wechsler, D. A. (1997). *Wechsler Memory Scale, 3rd Edn. Manual*. San Antonio, TX: Psychological Corporation.

Zack, M., and Poulos, C. X. (2009). Parallel roles for dopamine in pathological gambling and psychostimulant addiction. *Curr. Drug Abuse Rev.* 2, 11–25. doi: 10.2174/1874473710902010011

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Factor Analysis of the Brazilian Version of UPPS Impulsive Behavior Scale

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Objective: To examine the internal consistency and factor structure of the Brazilian adaptation of the UPPS Impulsive Behavior Scale.

Methods: UPPS is a self-report scale composed by 40 items assessing four factors of impulsivity: (a) urgency, (b) lack of premeditation; (c) lack of perseverance; (d) sensation seeking. In the present study 384 participants (278 women and 106 men), who were recruited from schools, universities, leisure centers and workplaces fulfilled the UPPS scale. An exploratory factor analysis was performed by using Varimax factor rotation and Kaiser Normalization, and we also conducted two confirmatory analyses to test the independency of the UPPS components found in previous analysis.

Results: Results showed a decrease in mean UPPS total scores with age and this analysis showed that the youngest participants (below 30 years) scored significantly higher than the other groups over 30 years. No difference in gender was found. Cronbach's alpha, results indicated satisfactory values for all subscales, with similar high values for the subscales and confirmatory factor analysis indexes also indicated a poor model fit. The results of two exploratory factor analysis were satisfactory.

Conclusion: Our results showed that the Portuguese version has the same four-factor structure of the original and previous translations of the UPPS.

Keywords: impulsivity, UPPS Impulsive Behavior Scale, psychometric, UPPS (urgency, lack of premeditation, lack of perseverance, sensation seeking), executive function

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INTRODUCTION

Impulsivity is an important aspect of personality and is a central role in many forms of psychopathology. In general, impulsivity has been broadly defined as quick unplanned actions that lead to thoughtless behaviors and a tendency to act with a lower level of planning compared to individuals of similar intellectual level (Moeller et al., 2001). The lack of consensus regarding the definition of impulsivity is probably one of the main reasons for the great variation of results among studies that assess impulsivity (Malloy-Diniz et al., 2009). Such inconsistencies hamper efforts to understand the role of impulsivity in many forms of psychopathology, such as, substance abuse (Verdejo-García et al., 2007) and bipolar disorder (Malloy-Diniz et al., 2011).

Impulsivity is present in several psychiatric conditions and predictor of severity of medical, employment, alcohol, drug, family/social, legal and psychiatric problems in individuals with substance dependence (Verdejo-García et al., 2007). For example, in patients with bipolar disorder, the manifestation of impulsivity has been linked to suicidal behavior, as well as activities with high output of negative consequences and low quality of life (Malloy-Diniz et al., 2009; Kim et al., 2013).

To validate the main existing models of impulsivity Whiteside and Lynam (2001) analyzed the responses of 437 undergraduates in 17 widely used measures of impulsivity. The study resulted in the four factors UPPS Impulsive Behavior Scale. The first factor is lack of premeditation, which is characterized by the inability to think about the consequences of a decision. The second factor relates to sensation seeking, which is the tendency of an individual to engage in exciting activities and the urge to live new experiences that may or may not be dangerous. The third factor is urgency that represents a tendency to act impulsively in the presence of negative emotions at the expense of long-term gains. The last factor is lack of perseveration, and is characterized by the difficulty of maintaining focus on a particular task.

The UPPS Impulsive Behavior Scale has been translated into many languages and has been found to have strong psychometric properties in French and German (i.e., internal consistency coefficients scale between 0.77 and 0.85) as well as exploratory and confirmatory factor analysis (CFA) replicating the original four factors (Van der Linden et al., 2006; Schmidt et al., 2008). The validation and structuring of the UPPS for the Brazilian student sample, will contribute for future analysis of researches of other cultures, and in the future it will assist in clinical profiling in Brazil.

For the reasons presented above, the current authors translated the UPPS to Portuguese (Sediyama et al., 2013). However, before the UPPS can be used in researches or clinical work in Brazil, the psychometric properties of the Portuguese UPPS have to be established. Therefore, the aim of the present study was to examine in a student sample the internal consistency and factor structure of Brazilian adaptation of the UPPS Impulsive Behavior Scale.

TABLE 1 | Cronbach's alpha coefficient, mean, and standard deviation.

Scale	Mean score (*SD*)	Range	α ($IC_{95\%}$)
Lack of premeditation	20.32 (5.72)	11–44	0.87 (0.86–0.89)
Urgency	28.75 (7.40)	12–47	0.85 (0.83–0.87)
Sensation seeking	28.98 (8.47)	11–48	0.84 (0.82–0.87)
Lack of perseverance	19.20 (4.56)	10–32	0.75 (0.72–0.79)

MATERIALS AND METHODS

Participants

The study analyzed 384 participants (278 women and 106 men) that were convenient sample recruited from schools, universities, leisure centers, and workplaces. The mean age for female participants was 31-years-old ($SD = 11.94$) while male participants had a mean age of 34 years of age ($SD = 13.89$). Participants did not meet criteria for any psychiatric disorder relating to the MINI-Plus v5.0 (Amorim, 2000). Criterion analyses excluded participants younger than 18 or older than 62 years, with illiteracy, and with reported neurological disorders (such as cerebrovascular accident and epilepsy).

The participants were approached to in class, and asked to participate in the research by filling in the UPPS scale, socio-demographic scale, and MINI-Plus 5.0 (Amorim, 2000). Each candidate took an average of 60 min to finish.

The data from this study have all been drawn and have received ethical approval from the local research ethics committee of the Federal University of Minas Gerais, number ETIC 553/08. All participants provided written consent agreeing to the conditions before taking part of the experiment.

Instruments

Portuguese Impulsive Behavior Scale (UPPS)

The original version (Whiteside and Lynam, 2001) was adapted to Portuguese by Sediyama (Sediyama et al., 2013). It is a self-report scale which consists of 45 items that address the four personality factors associated to impulsive behavior in a Likert-type format ranging from 1 to 4: (1) strongly agree, (2) partially agree; (3) partially disagree and (4) strongly disagree. Besides the total scores of impulsivity, the UPPS also provides the subscale scores of each subtype of impulsivity: lack of premeditation, urgency, sensation seeking and lack of perseverance.

Mini International Neuropsychiatric Interview (MINI Plus v.5)

The MINI Plus is a structured diagnostic interview compatible with DSM-III-R/IV and ICD-10. This instrument was developed for clinical practice and research in psychiatric and primary care settings. The MINI Plus is a more detailed version that mainly helps diagnose psychotic and mood disorders in DSM-IV (Amorim, 2000).

Statistical Analysis

Descriptive statistics were calculated by mean and standard deviation. Normality of data distribution was verified by the Kolmogorov–Smirnov test. The internal consistency of the scale

TABLE 2 | Fit indices for confirmatory factor analysis models.

	Number of items	Excluded items	χ^2	gl	χ^2/gl	CFI	TLI	RMSEA	Interpretation
AFE1	45	0	12820.84*	990	12.95	0.94	0.93	0.048 (0.044–0.052)	Not suitable
AFE2	42	20, 30, 43	1341.29*	699	1.92	0.94	0.93	0.050 (0.046–0.054)	Suitable

*$p < 0.05$.

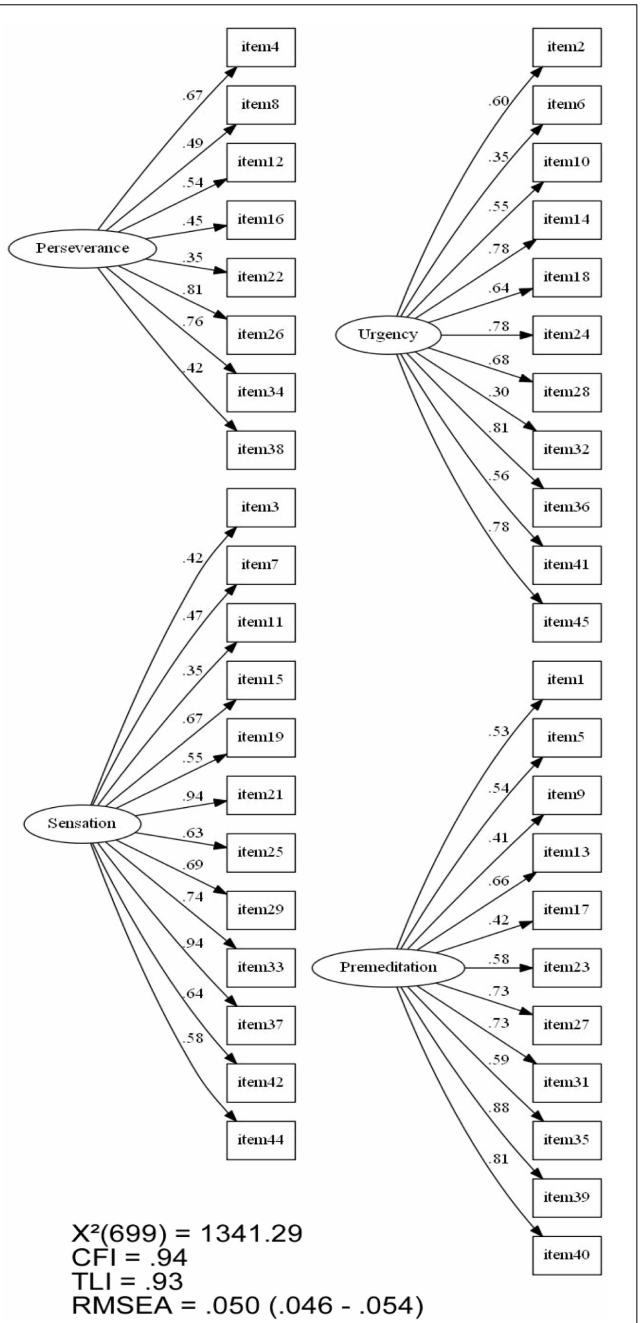

FIGURE 1 | Model fit indices for the final model by second exploratory factor analysis with factor loadings.

was calculated using the McDonald's omega and Cronbach's alpha. The One-way ANOVA with Tukey *post hoc* test were used to compare age groups. Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity were used for the evaluation of model sufficiency (Field, 2009). High values of KMO (more than 0.70) and values lower than 0.05 of significance of Bartlett's test probability indicate a satisfactory factor analysis (Field, 2009).

The analysis of the construct validity was done in two steps. First, a CFA was conducted to test the four-component structure of UPPS, with uncorrelated factors, found in previous studies (Magid and Colder, 2007). Second, an exploratory factor analysis (EFA) was performed. Weighted least squares method (WLSMV) estimator, once this estimator is recommended as a good alternative for items answered in an ordinal categorical scale (Chen et al., 2015). Geomin oblique rotation was used in EFA, and a range of indices were used to estimate how well the data fits the proposed model. These indexes included the chi-square and its corresponding *p*-value, the relative chi-square statistic, the root mean square error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker-Lewis Index (TLI). Here we used widely adopted guidelines to interpret the adequacy of model fit, considering χ^2/df index less than 2, and RMSEA of 0.08 or lower, and both CFI and TLI with a value of 0.90 (Brown, 2006; Kline, 2011).

RESULTS

Descriptive Statistics and Internal Consistency

A Kolmogorov–Smirnov test on the UPPS total scores indicated normal distribution of the data, $D = 0.03$, $p > 0.05$. In order to analyze the effect of age in UPPS scores the sample was divided in four age-groups: below 30, between 30 and 39, between 40 and 49, and above 50 years of live. Results showed a decrease in mean UPPS total scores with age, $F = 7.37$, $p < 0.001$. *Post hoc* analysis corrected for multiple comparisons showed that the youngest participants (below 30 years) scored significantly higher than the other groups (all p's < 0.05), and all other comparisons did not reveal significant differences (all p's > 0.05). Moreover, UPPS scores were also similar across gender, $t(244) = 1.09$, $p > 0.05$.

Answers to items 2, 3, 6, 7, 8, 10, 11, 14, 15, 18, 19, 21, 24, 25, 28, 29, 32, 33, 36, 37, 38, 21, 42, 44 and 45 (2 through 45), were reversed in order to keep the value of 1 corresponding to the lowest level of impulsivity, and the value of 4 to the highest level of impulsivity. Scores in the UPPS scale ranged from 49 to 139 points, with an average of 94.93 points (standard deviation = 15.39). **Table 1** shows means and standard deviation for each subscale of the UPPS.

Internal consistency of UPPS was assessed using McDonald's omega and Cronbach's alpha coefficient to measure scale reliability. For a structure with four factors, using maximum likelihood as the extraction method, the omega hierarchical

TABLE 3 | Factor correlation.

Factor	Lack of premeditation	Urgency	Sensation seeking	Lack of perseverance
Lack of premeditation	1			
Urgency	0.36	1		
Sensation seeking	0.11	0.09	1	
Lack of perseverance	0.48	0.17	0.08	1

(ω_h) was 0.40, suggesting that around 40% of test variance is attributable to a general factor common to all items. The omega total (ω_t), in turn, reached an index of 0.91, thus indicating that a large part of overall test variance (91%) is due to a general but also to the other four specific factors. Omega total (ω_t) for the individual factors were also high (ω_t factor 1 = 0.91; ω_t factor 2 = 0.88; ω_t factor 3 = 0.83; ω_t factor 4 = 0.74). Additionally, the Cronbach's alpha, results indicated satisfactory values for all subscales, with similar high values for the subscales; Lack of premeditation (0.87), Urgency (0.85), Sensation seeking (0.84), and a smaller value for the subscale Lack of perseverance (0.75). Item-total correlation (dropping corresponding items from total scores in order to avoid overestimated correlations) also corroborated these findings, as the coefficients were generally high (0.61 on average), and no item exhibited a coefficient less than 0.37 (**Table 1**).

Construct Validity

The Kaiser-Meyer-Olkin (KMO) coefficient showed a sufficient magnitude (0.86), and the sphericity Bartlett's test was significant ($p < 0.001$). First, we conducted a CFA on all items of the Brazilian version of UPPS. CFA evaluated the adequacy of fit of the orthogonal model four-factor solution. Results revealed a significant Chi-square statistic, $\chi^2 = 2424.15$, $p < 0.05$, $df = 939$, $\chi^2/df = 2/58$. Other CFA indexes also indicated a poor model fit, CFI = 0.87, TLI = 0.87, and RMSEA = 0.065 ($IC_{95\%} = 0.062$–0.068).

As CFA suggested that orthogonal model four-factor solution of the Brazilian version of UPPS was not suitable, the EFA was used to investigate the UPPS factorial structure.

As shown in **Table 2**, the initial EFA suggested that four-factor solution of the Brazilian version of UPPS was not suitable (see EFA1). Based on the Factor Loading, three items (20, 30, and 43) were excluded in the next analysis (EFA2) because showed large loading values in different factor than in the original theoretical structure.

The final version of four-factor solution of the Brazilian version of UPPS presented suitable (**Figure 1**) [$\chi^2_{(699)} = 1341.29$; $p < 0.001$; CFI = 0.94; TLI = 0.93; RMSEA = 0.050, with Geomin Rotated factor loadings greater or equal than 0.30 for all items].

Correlation between all four factors is present in **Table 3**. All latent variables but Sensation seeking correlated with at least one other variable. Similar findings were reported in previous studies (Van der Linden et al., 2006; Schmidt et al., 2008).

DISCUSSION

The present study showed that results supported the four factors of the Portuguese version, applied in a student sample, and it was consistent with previous research, that found the same factors in UPPS Impulsive Behavior Scale (Whiteside and Lynam, 2001; Magid and Colder, 2007). In addition, the consistency of UPPS demonstrated in omega score, poor homogeneity in the scale and the Cronbach's alpha, exploratory and CFA were satisfactory. These results are consistent with other translations that found internal consistency ranging from 0.75 to 0.87 (Van der Linden et al., 2006; Schmidt et al., 2008). Therefore, we can assume the four-dimensional structure and the distinct facets of Lack of premeditation, Urgency, Sensation seeking and Lack of perseverance as operationalized by the UPPS appear applicable to the Brazilian student population.

The adaptation of UPPS will provide an important tool for both clinical and research use. Since there's no scale in Brazilian context to assess this factors of impulsive behavior. In addition, the identification of these four facets corroborates the literature that impulsivity is a heterogeneous category that includes several different features. However, more studies should be conducted to assess the psychometric properties of the scale.

Like previous research that demonstrate lifespan changes in impulsivity, this study found differences in UPPS according to age, (Steinberg et al., 2008; Burnett et al., 2012). In relation to sex differences, we did not observe this in our sample, but it should be emphasized that in a prior study reported such differences, using a different version of the UPPS, the UPPS-P (Cyders et al., 2007). This study reported that male participants differed from female ones in relation to positive urgency and sensation seeking (Cyders, 2013). Our hypothesis is that study sample was larger ($n = 1{,}372$ undergraduates), and probably favored a robust statistical analysis in relation to the sex difference. However, it should be noted that our study undergoes limitations, such as the vast majority of female samples, a problem also observed in the original study (Whiteside and Lynam, 2001) and others (Van der Linden et al., 2006; Schmidt et al., 2008).

The range application in other contexts, such as psychiatric Brazilian samples is necessary to show evidence of effectiveness studies which include the UPPS, and for example, whether these factors differ according to the psychiatric diagnosis or can be predictive of some disorder. In summary, our study showed that the Portuguese version of the UPPS has adequate psychometric properties, similar to those reported in different cultures.

AUTHOR CONTRIBUTIONS

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

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REFERENCES

Amorim, P. (2000). Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. *Rev. Bras. Psiquiatr.* 22, 106–115. doi: 10.1590/S1516-44462000000300003

Brown, T. A. (2006). *Confirmatory Factor Analysis for Applied Research*. New York, NY: Guilford Press.

Burnett, H. S., Adam, R. J., Urner, M., van, L. L., Bahrami, B., Bays, P. M., et al. (2012). Impulsivity and rapid decision-making for reward. *Front. Psychol.* 3:153. doi: 10.3389/fpsyg.2012.00153

Chen, P. Y., Yang, C. M., and Morin, C. M. (2015). Validating the cross-cultural factor structure and invariance property of the insomnia severity index: evidence based on ordinal EFA and CFA. *Sleep Med.* 16, 598–603. doi: 10.1016/j.sleep.2014.11.016

Cyders, M. A. (2013). Impulsivity and the sexes: measurement and structural invariance of the UPPS-P impulsive behavior scale. *Assessment* 20, 86–97. doi: 10.1177/1073191111428762

Cyders, M. A., Smith, G. T., Spillane, N. S., Fischer, S., Annus, A. M., and Peterson, C. (2007). Integration of impulsivity and positive mood to predict risky behavior: development and validation of a measure of positive urgency. *Psychol. Assess.* 19, 107–118. doi: 10.1037/1040-3590.19.1.107

Field, A. P. (2009). *Discovering Statistics Using SPSS*. London: SAGE.

Kim, Y. S., Cha, B., Lee, D., Kim, S. M., Moon, E., Park, C. S., et al. (2013). The relationship between impulsivity and quality of life in euthymic patients with bipolar disorder. *Psychiatry Investig.* 10:246. doi: 10.4306/pi.2013.10.3.246

Kline, R. B. (2011). *Principles and Practice of Structural Equation Modelling*. London: The Guilford Press.

Magid, V., and Colder, C. R. (2007). The UPPS impulsive behavior scale: factor structure and associations with college drinking. *Pers. Individ. Dif.* 43, 1927–1937. doi: 10.1016/j.paid.2007.06.013

Malloy-Diniz, L. F., Neves, F. S., Abrantes, S. S. C., Fuentes, D., and Corrêa, H. (2009). Suicide behavior and neuropsychological assessment of type I bipolar patients. *J. Affect. Disord.* 112, 231–236. doi: 10.1016/j.jad.2008.03.019

Malloy-Diniz, L. F., Neves, F. S., de Moraes, P. H. P., De Marco, L. A., Romano-Silva, M. A., Krebs, M. O., et al. (2011). The 5-HTTLPR polymorphism, impulsivity and suicide behavior in euthymic bipolar patients. *J. Affect. Disord.* 133, 221–226. doi: 10.1016/j.jad.2011.03.051

Moeller, F. G., Barratt, E. S., Dougherty, D. M., Schmitz, J. M., and Swann, A. C. (2001). Psychiatric aspects of impulsivity. *Am. J. Psychiatry* 158, 1783–1793. doi: 10.1176/appi.ajp.158.11.1783

Schmidt, R. E., Gay, P., d' Acremont, M., and Van der Linden, M. A. (2008). German adaptation of the UPPS impulsive behavior scale: psychometric properties and factor structure. *Swiss J. Psychol.* 67, 107–112. doi: 10.1024/1421-0185.67.2.107

Sediyama, C. Y. N., Carvalho, A. M., Gauer, G., Tavares, N., Santos, R. M. M., Ginani, G., et al. (2013). Translation and adaptation of impulsive behavior scale (UPPS) to the Brazilian population. *Clin. Neuropsychiatry* 10, 79–85.

Steinberg, L., Albert, D., Cauffman, E., Banich, M., Graham, S., and Woolard, J. (2008). Age differences in sensation seeking and impulsivity as indexed by behavior and self-report: evidence for a dual systems model. *Dev. Psychol.* 44, 1764–1778. doi: 10.1037/a0012955

Van der Linden, M., d'Acremont, M., Zermatten, A., Jermann, F., Laroi, F., Willems, S., et al. (2006). A french adaptation of the UPPS impulsive behavior scale. *Eur. J. Psychol. Assess.* 22, 38–42. doi: 10.1027/1015-5759.22.1.38

Verdejo-García, A., Bechara, A., Recknor, E. C., and Pérez-García, M. (2007). Negative emotion-driven impulsivity predicts substance dependence problems. *Drug Alcohol Depend.* 91, 213–219. doi: 10.1016/j.drugalcdep.2007.05.025

Whiteside, S. P., and Lynam, D. R. (2001). The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Pers. Individ. Dif.* 30, 669–689. doi: 10.1016/S0191-8869(00)00064-7

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Working Memory Training and CBT Reduces Anxiety Symptoms and Attentional Biases to Threat: A Preliminary Study

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Research indicates that cognitive processes linked to the detection of threat stimuli are associated with poor attentional control, placing children and adolescents at increased risk for the development of anxious affect. The current study aimed to provide preliminary data to assess whether an intervention designed to improve attentional control (via working memory; WM) would lead to better performance in tests of WM and would be associated with positive changes in symptoms of trait and test anxiety, increased inhibitory control and reduced attention to threat. Forty adolescents aged 11–14 years who reported elevated anxiety and low attentional control were randomly allocated to a WM training or an active cognitive behavioural therapy (CBT) control group. Post intervention, WM training was associated with greater improvements (versus. CBT) in trained WM tasks. Both groups, however, reported fewer anxiety symptoms, demonstrated increased inhibitory control and a reduction in attentional biases to threat post intervention and these results were maintained at follow up. The study provides indicative evidence which suggests that WM training has similar benefits to a more traditional CBT intervention on reduced anxiety and attentional biases for threat. Future research should aim to replicate the findings in a large sample size and explore the broader impact of training on day-to-day functioning. In addition, further research is needed to identify which participants benefit most from different interventions (using baseline characteristics) on treatment compliance and outcome.

Keywords: anxiety, working memory, attentional control, intervention, attentional bias to threat, randomized control trial

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INTRODUCTION

Research suggests that clinical levels of anxiety are experienced by 2–15% of children and adolescents (Rapee et al., 2009). Anxiety follows a chronic pathway through development and is associated with several negative outcomes including lowered attendance at school (Richards and Hadwin, 2011; Wood et al., 2012), educational underachievement (Owens et al., 2008), poor peer relationships (Asendorpf et al., 2008) and increased risk for further mental and physical health difficulties (Roza et al., 2003). Researchers recognize that increased recruitment of attentional processes linked to regions of the prefrontal cortex (PFC) are important in the regulation of

negative affect (e.g., Banks et al., 2007; Hare et al., 2008; review by Graham and Milad, 2013). Theoretical frameworks of anxiety have increasingly focused on poor attentional control as one cognitive mechanism involved in the onset and maintenance of anxious affect (Eysenck and Calvo, 1992; Eysenck et al., 2007).

Cognitive theories aim to understand the nature and impact of anxiety-related impairments in attentional control on performance in cognitive tasks and on attention in daily life. Attentional Control Theory (Eysenck et al., 2007; Eysenck and Derakshan, 2011) for example, proposes that anxiety impacts core cognitive processes linked to inhibitory control (to resist interference from non-relevant distractors), set shifting (to move attention between relevant information or location) and updating information in WM (to remember and revise material for further processing). It suggests that the negative association between anxiety and cognition is most evident when attentional resources are directed toward external or internal threatening stimuli. Related theories similarly propose that elevated anxiety is associated with increased attention towards threat stimuli (e.g., Bar-Haim et al., 2007). Researchers have also argued that the allocation of attention to threat in anxiety leads to subsequent avoidance that works to help individuals regulate feelings of negative affect in the short term (Mogg and Bradley, 1998).

A substantial body of research has shown that children and adolescents with elevated anxiety rapidly focus attention on threat stimuli and demonstrate difficulties inhibiting task-irrelevant threat (Hare et al., 2008; Hadwin et al., 2009; Nightingale et al., 2010; Waters et al., 2012; review by Dudeney et al., 2015). Further research has found evidence of threat avoidance in childhood (Stirling et al., 2006) and adult anxiety (Horley et al., 2004). Attention processes associated with anxious affect have also been shown to predict anxiety over time in development. For example, poor attentional control at 6 years of age was associated with high stable and increasing anxiety trajectories across middle to late childhood (Duchesne et al., 2010). In addition, threat biases to angry (versus happy faces; as indicated in enhanced N170 amplitudes) were found to predict increased anxiety over time in children aged 5–7 years (O'Toole et al., 2013). Further studies have found that good attentional control moderates threat biases in anxiety. Susa et al. (2012), for example, found that a positive association between anxiety and attentional bias to threat was only evident in 9–14-year-old participants who reported low (versus high) levels of attentional control (see also Lonigan and Vasey, 2009 for similar results).

Attention bias modification (ABM) techniques were developed to reduce attentional biases to threat in anxiety using experimental paradigms that direct attention away from threatening stimuli or toward positive stimuli and where the overall aim is to reduce symptoms of anxious affect. Recent studies have found that ABM leads to reductions in attentional biases for threat and anxiety symptoms in children and adolescents (e.g., Rozenman et al., 2011; Eldar et al., 2012). For example, Eldar et al. (2012) conducted a randomised controlled trial (RCT) where participants aged 8–14 years completed four sessions of ABM (versus a placebo condition) over a 4 week period. The results showed reductions in attentional threat bias and clinician reported anxiety across the intervention period in the ABM (versus the placebo) group. Although significant reductions in parent and child report anxiety occurred across both groups. While a recent review outlined that further research is needed to understand the effectiveness of ABM in the reduction of anxiety (Lowther and Newman, 2014), studies have provided preliminary support for the development of interventions in children and adolescents to target anxiety symptoms via reduced attention to threat.

Further interventions have aimed to increase attentional control to reduce symptoms of psychopathology in development. These have largely focused on increasing WM capacity to impact inattention symptoms in children and adolescents diagnosed with attention deficit hyperactivity disorder (e.g., Beck et al., 2010; see review by Rabipour and Raz, 2012). WM is defined as a limited capacity system made up of the phonological loop, the visuospatial sketchpad (processing verbal versus visual and spatial information respectively), the central executive and the episodic buffer (suggested to act as an interface between current cognitive processing with information stored in long term memory; Baddeley, 2003). The central executive component of WM is proposed to form part of prefrontal processes that underpin attentional control (Baddeley, 2003; Kane and McVay, 2012). WM training has been linked to increased activation in prefrontal and parietal brain regions when completing WM tasks (Klingberg et al., 2002; Olesen et al., 2003; review by Bunge and Wright, 2007).

A recent review of training studies highlighted their utility in improving WM as well as attentional control more broadly (Jaeggi and Buschkuehl, 2014). Consistently, a recent meta-analysis reviewed 622 studies using one WM training programme (CogMed) and found evidence of moderate benefits (compared to passive control groups post intervention) and small to moderate benefits (between groups at follow-up) in WM capacity and inattention in daily life as reported by parents and teachers (Spencer-Smith and Klingberg, 2015[1]). Similarly, a meta-analysis of WM and executive function training more broadly (versus passive control groups) were reported to have beneficial effects in older adults on training tasks and wider executive attention (Karbach and Verhaeghen, 2014). Despite broadly positive outcomes for WM training, other reviews have highlighted some challenges within this literature linked to the longevity of effects and transfer to novel WM tasks or intelligence more broadly (Melby-Lervåg and Hulme, 2013).

Few studies have examined the impact of WM training on symptoms of negative affect. Owens et al. (2013) showed that WM training in adults who reported elevated symptoms of depression was associated with increased WM capacity (compared to a low level active control group). This improvement was reflected in greater event related potential (ERP) amplitudes as measured in contralateral delay activity following the intervention and where this component occurs around 300 ms after stimulus onset and is argued to reflect increased retention of remembered

[1]Note that a comment posted in the same journal and following the publication and re-analysis of data in this article argued that there was little evidence of WM training on positive change in daily life (Dovis et al., 2015).

items in visuospatial WM (see Ikkai et al., 2010). Consistent with this finding, an intervention study in 12- to 13-year-olds who were recognized to have social, emotional and behavioral difficulties demonstrated that a WM intervention (compared with a passive control group) increased performance in WM tasks and improved attentional control more broadly (as measured in a behavioral inhibition task). In addition, young people reported fewer symptoms of test anxiety following the intervention (Roughan and Hadwin, 2011). The possibility that a WM intervention can lower negative affect has significant implications for the development of translational research that increases attentional control to enable regulation of emotion and to allow individuals to meet goals in day-to-day life (see Bishop, 2007).

The current study aimed to provide preliminary data to test the proposition that interventions that work to increase attentional control (via improved WM) will have a positive effect on anxiety symptoms and attentional processes associated with negative affect (poor attentional control and attentional capture or avoidance of threat stimuli; Legerstee et al., 2010; Waters et al., 2012). Specifically, it assessed the impact of a WM intervention in adolescents who reported elevated anxiety symptoms and low attentional control. Previous work has reliably established that WM interventions show positive outcomes compared to passive control groups (review by Spencer-Smith and Klingberg, 2015). In addition, several researchers have highlighted that wait-list groups can overestimate treatment effects (e.g., Cunningham et al., 2013). Therefore, the current study compared a WM intervention to an active control group based on cognitive behavioural therapy (CBT); a widely accepted treatment of choice for anxiety (review by Cowart and Ollendick, 2010). Following previous research we anticipated that the CBT intervention would reduce anxiety symptoms in young people. We expected that the WM intervention should increase performance in WM tasks and that it would have a broader positive impact on key measures of attention (i.e., inhibitory control and attentional bias to threat), as well as feelings of anxious affect.

MATERIALS AND METHODS

Participants

Participants were 11–14 year olds from four secondary schools in the UK. One thousand, five hundred and sixty young people were invited to complete screening questionnaires and 640 individuals agreed to participate with parental consent. The only exclusion criterion was the documented presence of special educational needs, leading to the exclusion of 14 young people. Following exclusions and based on the screening inclusion criteria (see below), we identified and approached 146 young people who were eligible to take part and 40 individuals provided written assent and written parental consent to participate. Participants (mean age = 13 years, 0 months; 10 males; $N = 36$ White, $N = 1$ Asian and $N = 3$ Mixed Race.) were randomized to receive one of the two interventions. Appendix A in Supplementary Material outlines the flow of participants through each phase of the study.

Measures

Screening Measures

Participants completed two self-report questionnaires to assess anxiety and attentional control. Anxiety was measured using the 6-item generalized anxiety subscale from the Spence Children's Anxiety Scale (SCAS; Spence, 1998), with possible scores ranging from 0 to 18. Internal consistency in the screened sample was good ($\alpha = 0.84$). We screened attentional control using a 9-item questionnaire with possible scores ranging from 9 to 45; this measure included the seven items from the attention subscale on the Early Adolescent Temperament Questionnaire Revised (Ellis and Rothbart, 2001) and two additional items used to assess WM ability in a school or homework setting. The internal consistency of the scale in the screened sample was acceptable ($\alpha = 0.73$).

Individuals eligible to take part in the interventions scored above average (T-score > 50) on the anxiety questionnaire based on age and gender appropriate norms (scores of 6 or more for males and 7 or more for females) and scored at or below the median for the screened sample (Median = 31, $n = 640$) on the attentional control questionnaire. In the final sample, 27 participants scored in the 'elevated anxiety' range on the SCAS (T-score > 60, corresponding to scores of 9 or more) and 13 participants scored above average but below the elevated anxiety level (T-score > 50). The mean anxiety score in the screened sample ($n = 640$) was 5.79 ($SD = 3.92$, range = 0–18) and in the intervention group the mean was 11.15 ($SD = 3.52$, range = 6–17). Considering attentional control, respective means in the screened and the intervention samples were 5.32 ($SD = 5.32$, range = 15–44) and 26.50 ($SD = 26.50$, range = 20–31).

Outcome Measures

Outcome measures were completed at three time points: prior to the intervention (Time 1 – T1); within 3 weeks after the intervention (Time 2 – T2); between 3 and 4 months after the intervention (Time 3 – T3)[2] .

Working Memory

We measured near WM ability (tasks that were similar to taught tasks within the intervention) and distant WM ability (tasks that were not similar to taught tasks). Near tasks included a percentage correct composite score from the backward digit recall subtest and a modified (backward) version of the block recall subtest from the Working Memory Test Battery for Children (Pickering and Gathercole, 2001) to assess verbal and spatial WM, respectively. Participants heard a list of digits or saw a sequence of blocks of increasing length and were asked to repeat them in the reverse order.

Distant WM was assessed using the verbal and spatial versions of the computerized 2-n-back task (Shackman et al., 2006). In each task, an array of 34 letters was presented continuously for an entire block of trials. Each trial began with the appearance of a small square highlighting a subsection of the letters for 500 ms, followed by a 3500 ms interval in which the letter array was

[2]Participants also completed outcome measures for academic achievement, depression, and state and anxiety. The results associated with these measures were not a focus of the current paper and are therefore reported in Supplementary Analyses.

presented without the small square, followed immediately by the next trial. In the spatial task, participants pressed a button on each trial to indicate whether the location of the square was the same (matched trials) or different (mismatched trials) to the location of the square presented two trials earlier. In the verbal version, they indicated whether the type of letters inside the square was the same or different to the square presented two trials earlier. Each task included 18 matched trials and 54 mismatched trials. We calculated a composite score across tasks based on the percentage of accurate responses in the matched and mismatched trials.

Anxiety

The total score from the Revised Children's Manifest Anxiety Scale (RCMAS 2nd Edition; Reynolds and Richmond, 2008) was used to assess anxiety. The scale is made up of 40 items assessing physiological anxiety, worry and social anxiety. Participants answer each item with a yes/no response, generating possible scores from 0 to 40. The internal consistency for the total scale in the current sample was excellent ($\alpha = 0.90$, $n = 40$ at T1).

We used the total score from the Child Test Anxiety Scales to measure test anxiety (Wren and Benson, 2004). This scale includes 30 items to measure worry, physiological change and behaviors associated with taking tests. Participants are asked to indicate for each item (e.g., "I think most of my answers are wrong") whether they "almost never" (1), "some of the time" (2), "most of the time" (3) "to almost always" (4) show that behavior. The total score ranges from 30 to 120.

Inhibitory Control

Participants completed a computerized Stroop paradigm (Stroop, 1935) with 108 experimental trials. A trial consisted of a fixation cross for 500 ms, followed by a single word (BLUE, YELLOW, RED, or GREEN) or a horizontal string of Xs that disappeared upon response, followed by a blank screen for 1000 ms. The stimuli were typed in blue, yellow, red, or green font and participants pressed a button as quickly as possible to indicate the color of the font. There were three trial conditions presented with equal frequency and in a random order: (1) Congruent trials in which the word content and font color were matched; (2) Incongruent trials in which the word content and font color were mismatched; (3) Neutral trials in which participants were presented with a string of Xs in colored font. The dependent variable was an interference score in which mean RTs in the congruent condition were subtracted from mean RTs in the incongruent condition; positive scores indicate interference from incongruent information.

Attentional Bias to Threat

Participants completed a computerized dot probe task (MacLeod et al., 1986) consisting of 72 experimental trials. A trial started with a fixation cross for 500 ms, followed by a pair of faces presented for 500 ms, followed by a probe stimulus (two small dots) in the location of one of the previous faces until response, followed by a blank screen for 1000 ms. Participants indicated the orientation of the small dots (horizontal or vertical) as quickly as possible with a button press. The task included angry or neutral expressions portrayed by four models (two male, two female) from the NimStim set of facial expressions (Tottenham et al., 2009). The pair of faces in each trial was either angry-neutral (48 trials) or neutral-neutral (24 trials). There were three trial conditions that occurred with equal frequency and in a random order, where the probe replaced: (1) the angry face in angry-neutral pairs (congruent trials); (2) the neutral face in angry-neutral pairs (incongruent trials); (3) either of the faces in the neutral–neutral pairs (neutral trials). The dependent variable was an attentional bias score, calculated by subtracting the mean RT in the congruent condition from the mean RT in the incongruent condition; a positive score indicates a bias toward threat and a negative score indicates a bias away from threat. Scores that tend toward 0 indicate less interference from facial stimuli to meet task goals.

IQ

An estimate of full scale IQ was generated at T1 only using the matrix reasoning and vocabulary subtests from the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). In the vocabulary subtest, the participant simultaneously hears and sees a word and is asked to explain its meaning. In the matrix reasoning subtest, participants are shown a matrix of visual stimuli with one piece missing; they are required to select the missing visual stimulus from five response options.

Interventions

Working Memory Training (Cogmed RM, Pearson)

Twenty participants were randomly allocated to the WM training, which consists of 25 sessions completed 5 days per week for 5 weeks; participants completing at least 20 sessions over 8 weeks are regarded as complying with training. Each 30–45 min session includes eight computerized tasks that require visuo-spatial or verbal WM. Each activity includes 15 trials and the difficulty level (number of items to be remembered) is adjusted trial-by-trial. The program generates an 'index of improvement' which provides a measure of the progress made on one verbal and one visuo-spatial task over the training period. Previous work indicates that the mean index of improvement for children aged 7–17 years is 27 ($SD = 13$; Cogmed Coaching Manual).

Thirteen participants (Mean age = 13 years, 0 months; two male) met criteria for training compliance, attending a mean of 22.77 sessions ($SD = 2.52$, Range = 20–25) and achieving a mean index of improvement of 22.62 ($SD = 14.18$, Range = 6–49). Seven participants (Mean age = 13 years, 1 month; two male) did not complete training due to low motivation, attending a mean of 7.00 sessions ($SD = 4.16$, range = 1–15). Completers and non-completers were compared on T1 measures and significant differences between groups were observed for IQ, $t(18) = 2.95$, $p = 0.009$; IQ scores were significantly greater in the completers ($M = 100.08$, $SD = 5.91$, range = 88–108) compared with the non-completers ($M = 92.29$, $SD = 5.02$; Range = 86–99).

FRIENDS for Life (Barrett, 2005)

Twenty participants were randomly allocated to the CBT intervention, which consisted of 10 one-hour sessions conducted twice per week for 5 weeks. The intervention followed a manual which incorporates small group activities on feelings, thoughts,

relaxation techniques, problem solving and coping strategies. Nineteen participants (Mean age = 12 years, 11 months; six males) complied with training and attended a mean of 9.37 sessions ($SD = 0.83$, range = 8–10); one female participant did not comply with training due to scheduling difficulties and low attendance ($n = 4$ sessions).

Procedure

All aspects of the study were reviewed and approved by the internal university ethics and research governance procedures and complied with the ethical principles of the British Psychological Society. The screening questionnaires were administered in groups of 20–30 individuals during the school day supervised by teaching staff. Participants recruited into the interventions completed the outcome measures in two sessions during the school day at each time point. After completing T1 measures, participants were matched into pairs based on their RCMAS total anxiety scores. Using a computerized random number generator, one member of each pair was allocated to the WM group and the other member allocated to the CBT group by the second author who was blind to the identity or characteristics of the participants.

The WM training sessions were completed on a school or home computer; a trained Cogmed coach monitored progress following every completed session using the online system provided by Cogmed. The coach met with all participants who complied with training at least twice per week to provide motivation and feedback on progress. The CBT sessions were completed in small groups (4–6 individuals) in a classroom at school, led by a researcher trained to run the FRIENDS for Life program. Monetary reward were provided for both groups with £1 awarded for every session completed and an additional £5 awarded for participants completing all sessions.

Data Analysis

For each outcome measure (WM, anxiety, attentional control and attention to threat) we analyzed data between groups (WM, CBT) and over Time (T1, T2, T3) using repeated measures ANOVAs, where a group by time interaction would indicate a differential impact of the interventions over time. Exploratory data at T1 showed that IQ was correlated with WM scores ($r = 0.47$, $p = 0.01$ and $r = 0.37$, $p = 0.037$ for near and distant WM tasks respectively); therefore IQ was entered as a covariate in all WM analyses. For all analyses we report effect sizes and 95% confidence intervals around group means. The reported analyses are based on the participants who complied with training (completer analysis). For non-completers ($N = 8$), an intention-to-treat (ITT) analysis was also conducted for each outcome variable using the last-observation-carried-forward method (see Streiner, 2002). Five non-completers provided a full set of outcome measures at T1 only and the scores for these participants were carried forward to T2 and T3. Three non-completers provided outcome measures at all time points and these were used in the ITT analyses. All findings reported below for the completer analysis were replicated in the ITT analysis and these results are therefore not reported further. All statistical tests were two-tailed with an alpha level of 0.05.

RESULTS

Analyses were carried out to consider group differences in IQ and between IQ with outcome variables. There was no group difference in IQ ($t < 1$ and $p > 0.05$). **Table 1** presents the characteristics of the WM ($n = 13$) and CBT ($n = 19$) group at all three time points; there were no significant differences between the WM and CBT groups on any of the T1 measures in the completer or ITT samples (all ts > 1.5; ps > 0.1).

Training Effects

Working Memory (Near)

Analyses were carried out separately for the composite (spatial and verbal) WM near and distant scores. The repeated measures ANCOVA (controlling for IQ) on the percentage of trials correct in the near WM tasks showed a significant effect of group [$F(1,29) = 6.15$, $p = 0.019$, $\eta_p^2 = 0.18$][3] . The percentage of trials correct was higher in the WM group ($M = 55.16$, $SD = 8.73$, CI: 50.07 – 60.24) compared with the CBT group ($M = 47.14$, $SD = 10.43$, CI: 42.94 – 51.34). The main effect of time approached significance [$F(2,29) = 2.85$, $p = 0.066$, $\eta_p^2 = 0.09$], indicating a lower percentage of trials correct at T1 ($M = 47.16$, $SD = 8.99$, CI: 44.17 – 50.15) compared with T2 ($M = 52.72$, $SD = 12.81$, CI: 48.98 – 56.46) and T3 ($M = 53.56$, $SD = 11.89$, CI: 49.70 – 57.42) (T2 T3 ns.). The interaction between time and group was significant [$F(1,29) = 5.82$, $p = 0.005$, $\eta_p^2 = 0.17$], highlighting group differences at T2 ($M = 57.96$, $SD = 10.08$, CI:52.19 – 63.75 and $M = 47.47$, $SD = 12.50$, CI: 42.69 – 52.25 for the WM and CBT groups respectively) and T3 ($M = 58.58$, $SD = 10.53$, CI: 52.61 – 64.55 and $M = 48.54$, $SD = 10.98$, CI: 43.60 – 53.48 for the WM and CBT groups) respectively. The group difference at T1 (respective means: $M = 48.92$, $SD = 7.04$, CI: 44.29 – 53.54 and $M = 45.40$, $SD = 9.92$, CI: 41.58 – 49.23 was not significant; see **Figure 1**). Within group analyses for time were not significant for the WM group ($F < 2.5$, $p > 0.1$) or the CBT group ($F < 1$, $p > 0.1$).

Working Memory (Distant)

The repeated measures ANCOVA (controlling for IQ) on the percentage of trials correct in the distant WM tasks showed no main effect of group or time (Fs < 1, $p > 0.1$). In addition, the interaction between time and group was not significant ($F < 1.5$, $p > 0.1$); see **Figure 2**. The mean accuracy scores for the WM and CBT groups at T1, T2, and T3 were: 58.70, 68.61, 67.61, and 6.42, 64.41, 68.07; see **Figure 1**.

Anxiety Symptoms

For total anxiety symptoms the repeated measures ANOVA showed a main effect of time [$F(2,30) = 16.71$, $p < 0.001$, $\eta_p^2 = 0.36$], the mean anxiety scores at T2 ($M = 15.47$, $SD = 8.26$, CI: 12.83 – 18.84) and T3 ($M = 14.00$, $SD = 8.30$, CI:10.90 – 17.10) were significantly lower compared with T1 ($M = 19.96$, $SD = 31$, CI: 16.94–22.98) (T2 T3 ns following Bonferroni correction). There was no main effect of group and no interaction

[3] A *post hoc* power calculation for two independent samples and for a sample size of 13 for near WM tasks (related to mean T1T2 change in the WM group (mean = 9.29) versus the CBT group (mean = 1.90) indicated a power of 0.91.

TABLE 1 | Mean (SD) and range of working memory (WM) (% near and distant correct), anxiety symptoms, stroop interference score (ms), attentional bias score (ms) at measures at time 1 (T1- pre-intervention), time 2 (T2 – post-intervention) and time 3 (T3 – follow-up) in the WM and CBT groups.

	WM group**						CBT group#					
	T1		T2		T3		T1		T2		T3	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Working memory tasks												
Near	49.39	7.04	58.69	10.08	58.97	10.53	45.07	9.91	46.97	12.49	48.27	10.98
Distant	59.40	17.37	69.41	14.93	68.37	15.27	59.94	10.16	63.86	13.16	67.54	14.60
Anxiety measures												
Trait anxiety	21.92	7.33	17.76	7.15	14.00	7.30	18.00	8.76	13.89	8.78	14.00	9.09
Test anxiety	74.54	15.14	70.77	19.25	61.77	19.00	74.37	19.13	68.79	19.42	70.79	24.11
Attention measures												
Interference*	97.55	19.46	57.13	16.86	57.39	14.87	85.96	16.54	66.83	37.51	42.76	12.64

	Both groups ($n = 32$)					
	T1		T2		T3	
Bias toward@	44.61	35.63	6.42	41.03	−24.46	−24.46
Bias away	−38.53	30.44	15.15	59.23	12.89	12.89

***N = 13 participants; #N = 19 participants, *interference scores indicate the RT (ms) differences between incongruent versus congruent trial (increased positive scores reflect greater interference) and N = 18 participants completed the stroop test in the CBT group because one participant reported color blindness. @Indicates bias toward threat and bias away from threat collapsed across groups.*

between group and time ($Fs < 2.5$, $p > 0.1$; see **Figure 2**). With respect to test anxiety, the analysis showed a main effect of time [$F(2,30) = 4.73$, $p = 0.012$, $\eta_p^2 = 0.14$], highlighting more reported symptoms of test anxiety at T1 ($M = 74.43$, $SD = 17.35$, *CI*: 67.97 – 80.93) compared with T3 ($M = 66.28$, $SD = 22.30$, *CI*: 58.12 – 74.44). There was no difference between T1 and T2 ($M = 69.78$, $SD = 19.06$, *CI*: 62.67 – 76.89) or T2 and T3 test anxiety scores. There was no main effect of group ($F < 1$, $p > 0.1$). The interaction between group and time approached significance [$F(2,30) = 2.45$, $p = 0.095$, $\eta_p^2 = 0.08$]; indicating that there were no significant differences between any time point for the CBT group. However, for the WM group, time differences were evident between T3 with both other time points (T1 T2 ns; see **Figure 2**).

Inhibitory Control

Task performance

A one way (stimulus type: congruent, incongruent, neutral) repeated measures ANOVA on RTs in the Stroop task at T1 revealed a typical congruency effect. There was a main effect of stimulus type [$F(1.36,40.81) = 36.60$, $p < 0.001$, $\eta_p^2 = 0.55$], where RTs were significantly longer in the incongruent condition ($M = 806.12$ ms, $SD = 133.13$, $CI = 757 – 854$) compared with the congruent ($M = 715.29$ ms, $SD = 106.42$, $CI = 676 – 754$, $p < 0.001$) and neutral conditions ($M = 741.87$ ms, $SD = 111.27$, $CI = 701 – 782$, $p < 0.001$). RTs in the congruent conditions were also significantly faster than the RTs in the neutral condition ($p < 0.001$).

The repeated measures ANOVA on interference scores revealed no significant main effect of group and no interaction between group and time ($Fs < 1$, all $ps > 0.1$). There was a main effect of time [$F(2,60) = 51$, $p = 0.003$, $\eta_p^2 = 0.18$] showing significantly higher interference scores at T1 ($M = 90.82$ ms, $SD = 69.25$, $CI = 65 – 116$) compared with T2 ($M = 62.76$, $SD = 59.99$, $CI = 41 – 85$) and T3 ($M = 48.90$ ms, $SD = 53.23$, $CI = 29 – 68$); see **Figure 3**.

Threat Bias

Task performance

A one way (probe position: congruent, incongruent, neutral) repeated measures ANOVA was conducted on RTs in the dot probe paradigm at T1 in order to understand baseline task performance. The results revealed no significant effect of probe position on RTs ($F < 1$, $p > 0.1$; congruent: $M = 715.71$ ms, $SD = 163.63$; incongruent: $M = 716.25$ ms, $SD = 163.42$; neutral: $M = 722.15$ ms, $SD = 162.57$).

Considering group differences and attentional bias to threat, the results showed no effect of group [$F(1,30) = 2.14$, $p = 0.12$, $\eta_p^2 = 0.02$]. In addition, there was no main effect of time and the interaction between time and group was not significant (in both cases $F < 1$ and $p > 0.1$). The respective mean bias scores (and SD) for threat for the WM and CBT intervention groups at each time point was 15.97, ($SD = 64.90$, $CI = -14.43$ – 46.37), 17.23 ($SD = 51.94$, $CI = -11.93$ – 46.38), −2.26 ($SD = 59.75$, $CI = -33.03$ – 28.51) and −10.01 ($SD = 44.65$, $CI = -35.16$ – 15.13), 6.85 ($SD = 51.17$, $CI = -17.27$ – 30.97), −6.24 ($SD = 50.39$, $CI = -31.70$ – 19.21). Further exploration of the T1 attentional bias scores showed that across the two intervention groups there were two types of participant at baseline; those that attended toward threat (bias score > 0, $n = 15$) and those that attended away from threat (bias score < 0, $n = 17$). Therefore, analyses were run separately for the two types of threat bias. Because sample sizes were small analyses

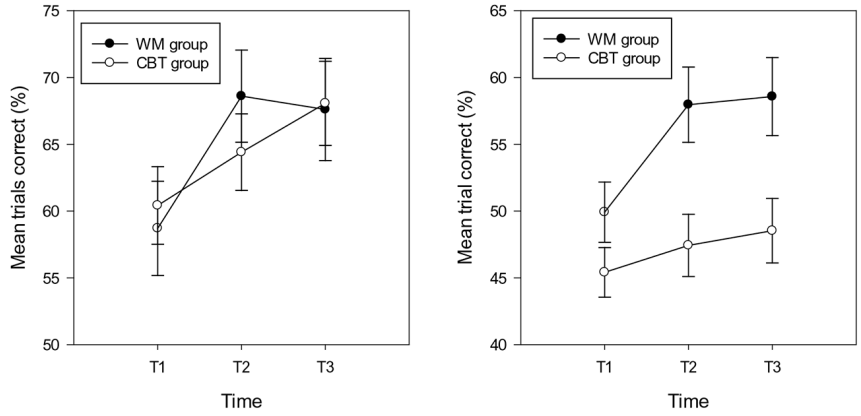

FIGURE 1 | Percentage of trials correct (and standard errors) in the near (right hand graph) and distant (left hand graph) working memory tasks in the WM and CBT intervention groups at each time point.

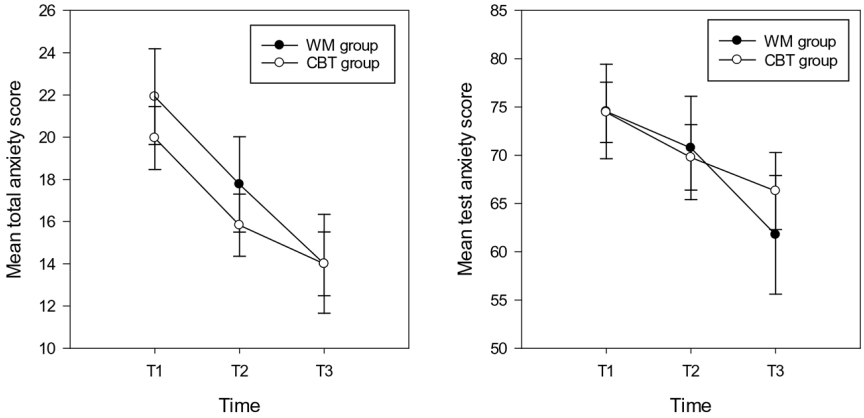

FIGURE 2 | Mean total anxiety scores (and standard errors) for total anxiety (left hand graph) and test anxiety (right hand graph) in the WM and CBT intervention groups at each time point.

were collapsed across groups to explore the effect of time on bias scores.[4]

For the participants who attended to threat at T1, the ANOVA revealed a main effect of time [$F(2,28) = 8.26$, $p = 0.002$, $\eta_p^2 = 0.37$], highlighting significantly higher bias scores at T1 ($M = 44.63$ ms, $SD = 35.64$, *CI*: 24.89 – 64.36) compared with T2 ($M = 6.42$, $SD = 41.03$, $p = 0.082$, *CI:*−16.29 – 29.14) and *T3* ($M = -24.46$ ms, $SD = 52.96$, $p = 0.008$, *CI*: −53.78 – 4.68). Considering each time point separately, one sample *t*-tests showed a significant bias toward threat at T1 [$t(14) = 4.85$, $p < 0.001$], no bias at T2 ($t < 1$, $p > 0.1$) and a marginal trend for a bias away from threat at T3 [$t(14) = 1.79$, $p = 0.095$; see **Figure 3**]. For participants who attended away from threat at T1, the repeated measures ANOVA revealed a main effect of time [$F(2,32) = 6.75$, $p = 0.004$, $\eta_p^2 = 0.30$] with significantly higher (avoidant) bias scores at T1 ($M = -38.36$ ms, $SD = 34.44$, *CI*: −56.07 – −20.65) compared with T2 ($M = 15.16$, $SD = 59.24$, *CI:*−15.29 – 45.61) and T3 ($M = 12.88$ ms, $SD = 48.93$, *CI:*−12.28 – 38.03). One sample *t*-tests indicated that there was a significant bias away from threat for this group of participants at T1 [$t(16) = 4.59$, $p < 0.001$], and no bias at T2 or T3 (*t*s < 1.5, $p > 0.1$); see **Figure 3**.

DISCUSSION

The current study provides preliminary evidence to demonstrate reductions in self-report anxiety symptoms, anxiety-related cognitive biases for threat and increased inhibitory control following WM and CBT interventions for adolescents who reported elevated anxious affect and low attentional control. In addition, the WM group showed better performance post intervention on tasks similar to those that were trained, compared to the CBT group. The findings link to previous intervention studies which have found that adults with elevated depression symptoms benefitted from a WM intervention to

[4]Note that the addition of the group in both analyses did not change the main effect of time and in both cases the main effect of group and the interaction between group and time was not significant (all *F*s < 1 and all *p*s > 0.1).

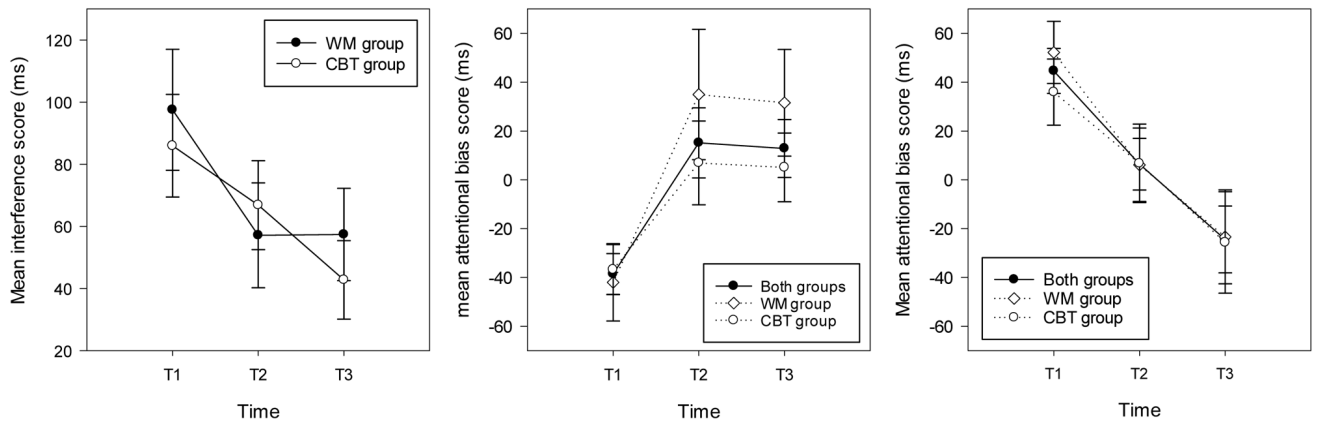

FIGURE 3 | Mean interference scores (and standard errors) in the stroop task (left hand graph) and attentional bias scores (and standard errors) in the WM group, the CBT and both groups combined for individuals attending toward threat (right hand graph) and away from threat (middle graph) at each time point.

show improved performance on WM tasks (Owens et al., 2013). In addition, they are consistent with research which has shown that young people with social and emotional behavioral difficulties who showed increased performance on WM tasks, better inhibitory control and fewer symptoms of test anxiety after completing a WM training intervention compared with a passive control group (Roughan and Hadwin, 2011). The current study extends previous research to show reduced attentional biases to threat following CBT and WM interventions. The findings fit with a broader literature highlighting the effectiveness of a WM training intervention on the reduction of symptoms associated with developmental psychopathology including inattention, hyperactivity and oppositional behavior (e.g., Klingberg et al., 2005; Beck et al., 2010).

Consistent with previous studies, the findings reported here showed reduced anxiety symptoms following a CBT intervention (e.g., Stallard et al., 2008). A recent meta-analysis highlighted that CBT is an effective treatment for anxiety reduction in children and adolescents compared to wait-list control groups (James et al., 2015). These authors noted, however, that few studies have compared CBT to active control groups receiving other forms of psychological intervention. The current study showed that the magnitude of the reduction in anxiety symptoms did not differ between the WM training and CBT intervention groups. They provide tentative evidence to suggest that attentional training could be a viable alternative or complementary intervention for children and adolescents with elevated anxious affect. Moreover, they fit with current studies suggesting that interventions that focus on attentional processes in anxiety might provide an important supplement to CBT and where this alternative approach could be most effective for individuals who are not responsive to more traditional treatment approaches (e.g., Bechor et al., 2014; review by Lowther and Newman, 2014).

The current study extends previous research to demonstrate that WM training and CBT led to increased inhibitory control post-intervention. In previous studies, wait-list control groups have shown relative stability in inhibitory control over a 3 months period (Roughan and Hadwin, 2011). Past research has not typically considered the impact of CBT on measures of attentional control. The current findings link to one study with adults with a clinical diagnosis of obsessive–compulsive disorder and who completed a CBT intervention. This group of adults showed cognitive deficits in set shifting, non-verbal memory and flexible behavior prior to treatment and these difficulties were no longer evident following CBT (Kuelz et al., 2006). In addition to improved inhibitory control, the current study found that across both groups adolescents showed reductions in attentional biases (characterized as biases toward or away from threat stimuli), indicating increased attention on task goals post intervention. This finding extends the previous literature (e.g., Waters et al., 2012) to indicate that reductions in attentional bias were not restricted to individuals completing CBT, but were also evident following a WM intervention.

Despite the growing emphasis on attentional control deficits in cognitive models of anxiety (e.g., Eysenck et al., 2007) and related research (Susa et al., 2012), the focus of recent interventions has been on modifying attentional biases to threat via ABM (e.g., Pérez-Edgar et al., 2014), rather than on improving attentional control more broadly. The results in the current study represent an important first step in the development of attention based interventions for adolescents who experience elevated anxiety. They suggest that biases for threat can be impacted via improved attentional control and in the absence of moderating attentional threat biases directly. Because improved attentional control and a reduction in threat biases was evident in both intervention groups, the results suggest that positive changes in anxiety symptoms can result from improved attentional control, as well as following more traditional CBT. Research with larger sample sizes would allow further examination of pathways to change via different interventions.

The proposition that increased attentional control (via WM training) can impact positively on anxiety symptoms

is consistent with a broader literature that has highlighted the role of the PFC in emotional regulation (e.g., Davidson et al., 2000). It also links to related studies that have found a negative association between PFC activation with brain regions linked to fearful responding, including the amygdala (Etkin et al., 2006; Hare et al., 2008). For example, research has demonstrated that adults who report elevated anxiety show reduced ability to utilize attentional processes associated with the PFC (including the Anterior Cingulate Cortex and the lateral PFC) and where this pattern of activation is argued to maintain threat biases in anxiety (Öhman, 2005; reviews by Bishop, 2007).

Previous research also suggests that the reduction in anxiety symptoms following CBT has been associated with increased activation of the PFC and associated improvements in emotional regulation when completing cognitive tasks. One goal of CBT is positive re-framing (Cowart and Ollendick, 2010). The reduction in attention biases in the current study following CBT links to studies which have found that positive re-appraisal of negative stimuli is associated with increased activation in the PFC and reduced activation in the amygdala. For example, Ochsner et al. (2002) asked participants to attenuate emotional responses to negative picture stimuli (versus inspect them as they typically would). They showed that brain activation in the Dorsolateral PFC was associated with stimulus reappraisal and where this process was inversely linked to amygdala activation (Ochsner et al., 2002; see also Banks et al., 2007). Consistent with this finding, Maslowsky et al. (2010) showed that following a CBT intervention young adolescents with a primary diagnosis of generalized anxiety disorder showed increased activation in the right ventrolateral PFC and the authors argued that this activation reflected top–down regulation of negative emotion following treatment. To understand mechanisms of change, future research using WM and CBT interventions would benefit further from exploring neurocognitive change following treatment (e.g., Owens et al., 2013).

The current study had a number of further strengths. The inclusion of a 3-months follow-up assessment was important in highlighting that improvements on all outcome measures were maintained over an extended period of time. A further notable finding of the current study was to identify baseline characteristics associated with drop-out from the WM intervention. The results indicated that completion of the WM intervention was particularly challenging for individuals with lower IQ, raising the possibility that a reduction in the intensity of the intervention (i.e., the frequency and duration of sessions) could be beneficial for some young people. While this finding was important, the challenges associated with the WM group led to the attrition rate being higher than the CBT group. Although there were no differences on baseline measures between the individuals completing each intervention, we cannot rule out the possibility that the WM group represented a particularly motivated group who were able to overcome the challenges of the WM training (see Jaeggi and Buschkuehl, 2014). A further limitation in the current study was the absence of a wait-list control group. Previous research has consistently shown benefits of WM and CBT training versus passive control groups (James et al., 2015; Spencer-Smith and Klingberg, 2015) and researchers have argued that their inclusion can exaggerate treatment effects (Cunningham et al., 2013). However, the inclusion of a passive control group in the context of scoping trials does have some benefit in understanding the stability of outcome attentional measures over time and in the absence of an intervention. These limitations highlight the need for larger scale studies with increased sample sizes to account for high attrition rates and that include WM, active control and passive control groups.

One further difficulty in the current study was the lack of generalization of WM training to untrained WM tasks. A recent meta-analysis concluded that there was evidence of reliable near transfer effects on measures of verbal and visuospatial WM in the short term after training; however, there was no evidence of distant transfer effects on measures of cognitive ability or educational achievement (Melby-Lervåg and Hulme, 2013). It is possible that the current distant WM tasks utilized in the current study were not sensitive to differences between interventions, therefore, future research should aim to ensure that a range of untrained tasks is included in the evaluation of WM interventions. In addition, the current study focused on trait measurements of anxiety. And Supplementary Analysis revealed a mixed profile on outcomes linked to additional measures of negative affect and educational achievement. Though preliminary, they showed no effect of either intervention on self-report state anxiety, though some positive change in symptoms of depression and achievement scores in both groups. Consistent with theoretical accounts of anxiety, a recent review argued that state anxiety can moderate the impact of trait anxiety on attentional tasks, making it an important index of treatment outcome (Robinson et al., 2013). Moreover, it highlighted the complex association between anxiety and performance on WM tasks and where better performance can reflect increased individual effort and/or task cognitive load (see also Eysenck and Derakshan, 2011). Future research should aim to capture potential performance moderators using objective measures of effort and emotional regulation.

CONCLUSION

The current study outlines preliminary data which indicates that both WM and CBT interventions were effective in reducing anxiety symptoms in young people. While the study reflects a small sample size, its findings support the notion of a "proof of concept" in training WM (Gathercole et al., 2012) that indicate a broader positive impact on increased inhibitory control and attentional biases for threat. The novel findings should encourage the use of larger scale replication RCTs in clinical and educational settings that place greater emphasis on understanding the key mechanisms of change, as well the impact of baseline characteristics on attrition and treatment outcomes (Jaeggi and Buschkuehl, 2014).

AUTHOR CONTRIBUTIONS

Both authors made substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fpsyg.2016.00047

REFERENCES

Asendorpf, J. B., Denissen, J. J., and van Aken, M. A. (2008). Inhibited and aggressive preschool children at 23 years of age: personality and social transitions into adulthood. *Dev. Psychol.* 44, 997–1011. doi: 10.1037/0012-1649.44.4.997

Baddeley, A. D. (2003). Working memory: looking back and looking forward. *Nat. Rev. Neurosci.* 4, 829–839. doi: 10.1038/nrn1201

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., and Phan, K. L. (2007). Amygdala–frontal connectivity during emotion regulation. *Soc. Cogn. Affect. Neurosci.* 2, 303–312. doi: 10.1093/scan/nsm029

Bar-Haim, Y., Lamy, D., Pergamin, L., Bekermans-Kranenburg, M. J., and van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol. Bull.* 133, 1–24. doi: 10.1037/0033-2909/133.1.1

Barrett, P. (2005). *FRIENDS for Life: Workbook for Youth*. Bowen Hills: Australian Academic Press.

Bechor, M., Pettit, J. W., Silverman, W. K., Bar-Haim, Y., Abend, R., Pine, D. S., et al. (2014). Attention bias modification treatment for children with anxiety disorders who do not respond to cognitive behavioural therapy: a case series. *J. Anxiety Disord.* 28, 154–159. doi: 10.1016/j.janxdis.2013.09.001

Beck, S. J., Hanson, C. A., Puffenberger, S. S., Benninger, K. L., and Benninger, W. B. (2010). A controlled trial of working memory training for children and adolescents with ADHD. *J. Clin. Child Adolesc. Psychol.* 39, 825–836. doi: 10.1080/15374416.2010.517162

Bishop, S. J. (2007). Neurocognitive mechanisms of anxiety: an integrative account. *Trends Cogn. Neurosci.* 11, 307–316. doi: 10.1016/j.tics.2007.05.008

Bunge, S. A., and Wright, S. B. (2007). Neurodevelopmental changes in working memory and cognitive control. *Curr. Opin. Neurobiol.* 17, 243–250. doi: 10.1016/j.conb.2007.02.005

Cowart, M. J. W., and Ollendick, T. H. (2010). "Attentional biases in children: implications for treatment," in *Information Processing Biases and Anxiety: A Developmental Perspective*, eds J. A. Hadwin and A. P. Field (Chichester: Wiley-Blackwell), 297–319.

Cunningham, J. A., Kypri, K., and McCambridge, J. (2013). Exploratory randomized controlled trial evalutating the impact of a waiting list control design. *BMC Med. Res. Methodol.* 13:150. doi: 10.1186/1471-2288-13-150

Davidson, R. J., Jackson, D. C., and Kalin, N. H. (2000). Emotion, plasticity, context, and regulation: Perspectives from affective neuroscience. *Psychol. Bull.* 126, 890–909. doi: 10.1037/0033-2909.126.6.890

Dovis, S., Agelink van Rentergem, J., and Huizenga, H. M. (2015). Does cogmed working memory training really improve inattention in daily life? A reanalysis. *PLoS ONE* 10:e85992.

Duchesne, S., Larose, S., Vitaro, F., and Tremblay, R. E. (2010). Trajectories of anxiety in a population sample of children: clarifying the role of children's behavioral characteristics and maternal parenting. *Dev. Psychopathol.* 22, 361–373. doi: 10.1017/S0954579410000118

Dudeney, J., Sharpe, L., and Hunt, C. (2015). Attentional bias towards threatening stimuli in children with anxiety: a meta-analysis. *Clin. Psychol. Rev.* 40, 66–75. doi: 10.1016/j.cpr.2015.05.007

Eldar, S., Apter, A., Lotan, D., Edgar, K. P., Naim, R., Fox, N. A., et al. (2012). Attention bias modification treatment for pediatric anxiety disorders: a randomized controlled trial. *Am. J. Psychiatry* 169, 213–220. doi: 10.1176/appi.ajp.2011.11060886

Ellis, L. K., and Rothbart, M. K. (2001). Revision of the Early Adolescent Temperament Questionnaire. *Poster presented at the 2001 Biennial Meeting of the Society for Research in Child Development*, Minneapolis, MN.

Etkin, A., Egner, T., Peraza, D. M., Kandel, E. R., and Hirsch, J. (2006). Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron* 51, 871–882. doi: 10.1016/j.neuron.2006.07.029

Eysenck, M. W., and Calvo, M. G. (1992). Anxiety and performance: the processing efficiency theory. *Cogn. Emot.* 6, 409–434. doi: 10.1080/02699939208409696

Eysenck, M. W., and Derakshan, N. (2011). New perspectives in attentional control theory. *Pers. Individ. Dif.* 50, 955–960. doi: 10.1016/j.paid.2010.08.019

Eysenck, M. W., Derakshan, N., Santos, R., and Calvo, M. G. (2007). Anxiety and cognitive performance: attentional control theory. *Emotion* 7, 336–353. doi: 10.1037/1528-3542.7.2.336

Gathercole, S. E., Dunning, D. L., and Holmes, J. (2012). Cogmed training: let's be realistic about intervention research. *J. Appl. Res. Mem. Cogn.* 1, 201–203. doi: 10.1016/j.jarmac.2012.06.003

Graham, B. M., and Milad, M. R. (2013). "Prefrontal cortex regulation of emotion and anxiety," in *Neurobiology of Mental Illness*, 4th Edn, eds D. S. Charney, P. Skar, J. D. Buxbaum, and E. J. Nestler (Oxford: Oxford University Press), 580–592.

Hadwin, J. A., Donnelly, N., Richards, A., French, C. C., and Patel, U. (2009). Childhood anxiety and attention to emotion faces in a modified Stroop task. *Br. J. Dev. Psychol.* 27, 487–494. doi: 10.1348/026151008X315503

Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., and Casey, B. J. (2008). Biological substrates of emotional reactivity in adolescence during a go-nogo task. *Biol. Psychiatry* 63, 927–934. doi: 10.1016/j.biopsych.2008.03.015

Horley, K., Williams, L. M., Gonsalvez, C., and Gordon, E. (2004). Face to face: visual scanpath evidence for abnormal processing of facial expressions in social phobia. *Psychiatry Res.* 127, 43–53. doi: 10.1016/j.psychres.2004.02.016

Ikkai, J., McCollough, A. W., and Vogel, E. K. (2010). Contralateral delay activity provides a neural measure of the number of representations in visual working memory. *J. Neurophysiol.* 103, 1963–1968. doi: 10.1152/jn.00978.2009

Jaeggi, S. M., and Buschkuehl, M. (2014). "Working memory training and transfer: theoretical and practical considerations," in *New Frontiers of Multidisciplinary Research in Steam-H*, ed. B. Toni (Cham: Springer International Publishing), 19–43.

James, A. C., James, G., Cowdrey, F. A., Soler, A., and Choke, A. (2015). *Cognitive Behavioural Therapy for Anxiety Disorders in Children and Adolescents*. Hoboken, NJ: John Wiley & Sons Ltd.

Kane, M. J., and McVay, J. C. (2012). What mind wandering reveals about executive-control abilities and failures. *Curr. Dir. Psychol. Sci.* 21, 348–354. doi: 10.1177/0963721412454875

Karbach, J., and Verhaeghen, P. (2014). Making working memory work: a meta-analysis of executive-control and working memory training

in older adults. *Psychol. Sci.* 25, 2027–2037. doi: 10.1177/0956797614548725

Klingberg, T., Fernell, E., Olesen, P. J., Johnson, M., Gustafsson, P., Dahlstrom, K., et al. (2005). Computerized training of working memory in children with ADHD: a randomized controlled trial. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 177–186. doi: 10.1097/00004583-200502000-00010

Klingberg, T., Forssberg, H., and Westerberg, H. (2002). Increased brain activity in frontal and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *J. Cogn. Neurosci.* 14, 1–10. doi: 10.1162/089892902317205276

Kuelz, A. K., Riemann, D., Halsband, U., Vielhaber, K., Unterrainer, J., Kordon, A., et al. (2006). Neuropsychological impairment in obsessive compulsive disorder: improvement over the course of cognitive behavioral treatment. *J. Clin. Exp. Neuropsychol.* 28, 1273–1287. doi: 10.1080/13803390500507246

Legerstee, J. S., Tulen, J. H., Dierckx, B., Treffers, P. D., Verhulst, F. C., and Utens, E. M. (2010). CBT for childhood anxiety disorders: differential changes in selective attention between treatment responders and non-responders. *J. Child Psychol. Psychiatry* 51, 162–172. doi: 10.1111/j.1469-7610.2009.02143.x

Lonigan, C. J., and Vasey, M. W. (2009). Negative affectivity, effortful control, and attention to threat-relevant stimuli. *J. Abnorm. Child Psychol.* 37, 387–399. doi: 10.1007/s10802-008-9284-y

Lowther, H., and Newman, E. (2014). Attention bias modification (ABM) as a treatment for child and adolescent anxiety: a systematic review. *J. Affect. Disord.* 168, 125–135. doi: 10.1016/j.jad.2014.06.051

MacLeod, C., Mathews, A., and Tata, P. (1986). Attentional bias in emotional disorders. *J. Abnorm. Psychol.* 95, 15–20. doi: 10.1037/0021-843X.95.1.15

Maslowsky, J., Mogg, K., Bradley, B. P., McClure-Tone, E., Ernst, M., Pine, D. S., et al. (2010). A preliminary investigation of neural correlates of treatment in adolescents with generalized anxiety disorder. *J. Child Adolesc. Psychopharmacol.* 20, 105–111. doi: 10.1089/cap.2009.0049

Melby-Lervåg, M., and Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Dev. Psychol.* 49, 270–291. doi: 10.1037/a0028228

Mogg, K., and Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behav. Res. Ther.* 36, 809–848. doi: 10.1016/S0005-7967(98)0g0063-1

Nightingale, Z. C., Field, A. P., and Kindt, M. (2010). "The emotional Stroop task in anxious children," in *Information Processing Biases and Anxiety: A Developmental Perspective*, eds J. A. Hadwin and A. P. Field (Chichester: Wiley-Blackwell), 47–75.

Ochsner, K. N., Bunge, S. A., Gross, J. J., and Gabrieli, J. D. E. (2002). Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J. Cogn. Neurosci.* 14, 1215–1229. doi: 10.1162/089892902760807212

Öhman, A. (2005). The role of the amygdala in human fear: automatic detection of threat. *Psychoneuroendocrinology* 30, 953–958. doi: 10.1016/j.psyneuen.2005.03.019

Olesen, P., Westerberg, H., and Klingberg, T. (2003). Increased prefrontal and parietal activity after training of working memory. *Nat. Neurosci.* 7, 75–79. doi: 10.1038/nn1165

O'Toole, L. J., DeCicco, J. M., Berthod, S., and Dennis, T. A. (2013). The N170 to angryfaces predicts anxiety in typically developing children over a two-year period. *Dev. Neurosci.* 38, 352–362. doi: 10.1080/87565641.2013.802321

Owens, M., Koster, E. H. W., and Derakshan, N. (2013). Improving attention control in dysphoria through cognitive training: transfer effects on working memory capacity and filtering efficiency. Psychophysiology 50, 297–307. doi: 10.1111/psyp.12010

Owens, M., Stevenson, J., Norgate, R., and Hadwin, J. A. (2008). Processing efficiency theory in children: working memory as a mediator between trait anxiety and academic performance. *Anxiety Stress Coping* 21, 417–430. doi: 10.1080/10615800701847823

Pérez-Edgar, K., Taber-Thomas, B., Auday, E., and Morales, S. (2014). Temperament and attention as core mechanisms in the early emergence of anxiety. *Contrib Hum Dev.* 26, 42–56. doi: 10.1159/000354350

Pickering, S., and Gathercole, S. (2001). *Working Memory Test Battery for Children (WMTB-C)*. Harlow: Pearson Education Ltd.

Rabipour, S., and Raz, A. (2012). Training the brain: fact and fad in cognitive and behavioural remediation. *Brain Cogn.* 79, 159–179. doi: 10.1016/j.bandc.2012.02.006

Rapee, R. M., Schniering, C. A., and Hudson, J. L. (2009). Anxiety disorders during childhood and adolescence: origins and treatment. *Annu. Rev. Clin. Psychol.* 5, 311–341. doi: 10.1146/annurev.clinpsy.032408.153628

Reynolds, C. R., and Richmond, B. O. (2008). *Revised Children's Manifest Anxiety Scale*, 2nd Edn. North York, ON: Multi-Health Systems Inc.

Richards, H. J., and Hadwin, J. A. (2011). An exploration of the relationship between trait anxiety and school attendance in young people. *School Mental Health* 3, 236–244. doi: 10.1007/s12310-011-9054-9

Robinson, O. J., Vytal, K., Comwell, B. R., and Grillon, C. (2013). The impact of anxiety upon cognition: perspectives from human threat of shock studies. *Front. Hum. Neurosci.* 7:203. doi: 10.3389/fnhum.2013.00203

Roughan, L., and Hadwin, J. A. (2011). The impact of working memory training in young people with social, emotional and behavioural difficulties. *Learn. Individ. Dif.* 21, 759–764. doi: 10.1016/j.lindif.2011.07.011

Roza, S. J., Hofstra, M. B., Van Der Ende, J., and Verhulst, F. C. (2003). Stable prediction of mood and anxiety disorders based on behavioral and emotional problems in childhood: a 14-year follow-up during childhood, adolescence, and young adulthood. *Am. J. Psychiatry* 60, 2116–2121. doi: 10.1176/appi.ajp.160.12.2116

Rozenman, M., Weersing, V. R., and Amir, N. (2011). A case series of attention modification in clinically anxious youths. *Behav. Res. Ther.* 49, 324–330. doi: 10.1016/j.brat.2011.02.007

Shackman, A. J., Sarinopoulos, I., Maxwell, J. S., Pizzagalli, D. A., Lavric, A., and Davidson, R. J. (2006). Anxiety selectively disrupts visuospatial working memory. *Emotion* 6, 40–61. doi: 10.1037/1528-3542.6.1.40

Spence, S. H. (1998). A measure of anxiety symptoms among children. *Behav. Res. Ther.* 36, 545–566. doi: 10.1016/S0005-7967(98)00034-5

Spencer-Smith, M., and Klingberg, T. (2015). Benefits of a working memory training programme for inattention in daily life: a systematic review and metaanalysis. *PLoS ONE* 10:e0119522. doi: 10.1371/journal.pone.0119522

Stallard, P., Simpson, N., Anderson, S., and Goddard, M. (2008). The FRIENDS emotional health prevention programme: 12 month follow-up of a universal UK school based trial. *Eur. Child Adolesc. Psychiatry* 17, 283–289. doi: 10.1007/s00787-007-0665-5

Stirling, L. J., Eley, T. C., and Clark, D. M. (2006). Preliminary evidence for an association between social anxiety symptoms and avoidance of negative faces in school-age children. *J. Clin. Child Adolesc. Psychol.* 35, 440–445. doi: 10.1207/s15374424jccp3503_9

Streiner, D. L. (2002). The case of the missing data: methods of dealing with dropouts and other research vagaries. *Can. J. Psychiatry* 47, 68–75.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi: 10.1037/h0054651

Susa, G., Pitica, I., Benga, O., and Miclea, M. (2012). The self regulatory effect of attentional control in modulating the relationship between attentional biases toward threat and anxiety symptoms in children. *Cogn. Emot.* 26, 1069–1083. doi: 10.1080/02699931.2011.638910

Tottenham, N., Tanaka, J. W., Leon, A. C., McCarry, T., Nurse, M., Hare, T. A., et al. (2009). The NimStim set of facial expressions: judgments from untrained research participants. *Psychiatry Res.* 168, 242–249. doi: 10.1016/j.psychres.2008.05.006

Waters, A. M., Mogg, K., and Bradley, B. P. (2012). Direction of threat attention bias predicts treatment outcome in anxious children receiving cognitive-behavioural therapy. *Behav. Res. Ther.* 50, 428–434. doi: 10.1016/j.brat.2012.03.006

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. London: Pearson Ltd.

Wood, J. J., Lynne, S. D., Langer, D. A., Wood, P. A., Clark, S. L., Eddy, J. M., et al. (2012). School attendance problems, and youth psychopathology: structural cross-lagged regression models in three longitudinal datasets. *Child Dev.* 83, 351–366. doi: 10.1111/j.1467-8624.2011.01677.x

Wren, D. J., and Benson, J. (2004). Measuring test anxiety in children: scale development and internal construct validation. *Anxiety Stress Coping* 17, 227–240. doi: 10.1080/10615800412331292606

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Enhancing Executive Function and Neural Health in Bipolar Disorder through Reasoning Training

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Cognitive deficits in executive function and memory among individuals with bipolar disorder (BD) are well-documented; however, only recently have efforts begun to address whether such cognitive deficits can be ameliorated through cognitive training. This pilot study examined the effects of a top–down, cognitive reasoning training program in adults with BD on both brain and cognitive measures. Twenty-seven participants (11 males, 16 females), aged 21–70 years old, completed the study. Participants completed neurocognitive testing and functional magnetic resonance imaging (fMRI) before and after training, consisting of 8 h (2 h/week) of training in small groups. The training delivered information processing strategies that were implemented and applicable to a variety of daily living contexts. Results indicated that participants showed significant gains in the primary outcome measure of complex abstraction, also referred to as gist reasoning, as well as in untrained domains of executive function and memory. We found a significant increase in resting cerebral blood flow (CBF) in left inferior frontal gyrus after cognitive training. We also found that resting CBF in the right frontal middle gyrus correlated positively with performance on the measure of complex abstraction. This feasibility study provides promising evidence that short-term reasoning training can enhance cognitive performance and brain health in adults with BD. These data motivate further efforts to explore adjuvant therapeutics to improve cognitive performance and underlying brain systems in bipolar, as well as other psychiatric disorders. Clinicaltrials.gov Identifier: NCT02843282, http://www.clinicaltrials.gov/ct2/show/NCT02843282

Keywords: bipolar disorder, cerebral blood flow, cognition, cognitive training, executive function, frontal networks, memory

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INTRODUCTION

Bipolar disorder (BD), a mental illness with recurring episodes of mania and depression, can have far-reaching detrimental effects on the everyday function and living of those with the diagnosis. In addition to causing distressing shifts in mood and energy level, we now know that patients with BD experience cognitive deficits, not only during mood episodes but also in remission (van Gorp et al., 1998; Quraishi and Frangou, 2002; Martinez-Aran et al., 2004). A meta-analysis of cognitive deficits in adult euthymic patients with BD (i.e., neither depressed nor manic) consistently found deficits in executive function and verbal learning, with variance in deficits across other areas of

cognition, such as memory, abstraction, set-shifting, sustained attention, and inhibition (Robinson and Ferrier, 2006). Robinson's study also suggested such cognitive deficits in euthymic individuals with BD are consistent across cultures (Robinson and Ferrier, 2006).

Imaging studies also reveal underlying neural abnormalities, including changes in brain blood flow and activation. For instance, O'Connell et al. (1995) examined cerebral blood flow (CBF) in BD and identified decreased CBF in prefrontal cortex during unipolar and bipolar depression, with schizophrenic and manic bipolar individuals exhibiting even greater hypofrontality. Benabarre et al. (2005) further supported this finding of hypofrontality by correlating poorer performance in executive function and memory with low perfusion in the frontal region. Resting state functional imaging studies of individuals with BD demonstrate abnormal activation in the prefrontal and cingulate cortices (Blumberg et al., 2003; Phillips et al., 2003, 2008; Kronhaus et al., 2006; Green et al., 2007). Other studies, including a quantitative meta-analysis review of functional magnetic resonance imaging studies in BD, extend previous evidence of attenuated activation of the left inferior frontal gurus (IFG) across emotional and cognitive tasks (Phillips et al., 2008; Chen et al., 2011). Whereas cognitive and brain abnormalities in both symptomatic and asymptomatic individuals with BD are well-documented, available clinical interventions continue to be limited to pharmacological and/or psychological counseling regimens to manage symptoms. These approaches will continue to be a vital aspect of BD treatment; however, additive benefits may be derived from protocols that directly address the common cognitive sequelae.

Emerging research has examined whether individuals with BD benefit from non-pharmacological approaches to improve the cognitive symptom complex of BD, such as cognitive training, with promising results suggesting an array of potential gains in performance (Deckersbach et al., 2010; Preiss et al., 2013; Torrent et al., 2013). Previously reported studies have implemented cognitive training alone or in conjunction with other symptom management and therapeutic interventions (e.g., mood management and psychoeducation) (Deckersbach et al., 2010; Preiss et al., 2013; Torrent et al., 2013; Demant et al., 2015). The cognitive training portion of these studies targeted specific processing deficits in BD, such as memory, executive function, and attention. Studies by Deckersbach et al. (2010) and Preiss et al. (2013) resulted in significant cognitive and mood improvement after training, specifically with gains on measures of executive function and reductions in reported depressive symptoms. On the other hand, similarly well-constructed studies to address cognitive and psychosocial deficits in BD failed to find significant improvement in cognitive function (Torrent et al., 2013; Demant et al., 2015). While cognitive gains were not reported, the Torrent et al. (2013) participants did exhibit significantly improved scores on a functional outcome measure. These studies, while varied in results, support the rationale for investigating component-specific cognitive training with individuals with BD.

Based on this foundation of evidence that targeting specific cognitive processes may benefit individuals with BD, we were interested in testing whether a top–down strategy-based cognitive training of integrative processes could reap brain and cognitive gains as has been uncovered in other populations (Gamino et al., 2010; Vas et al., 2011, 2016a; Mudar et al., 2013; Cook et al., 2014; Chapman et al., 2015). We were particularly interested in measuring the benefits of gist-reasoning training, which we will refer to as 'reasoning training,' in this population since prior work has shown reasoning training to generalize to other cognitive domains more than targeting specific processes, albeit in different populations (Gamino et al., 2010; Vas et al., 2011, 2016a; Mudar et al., 2013; Cook et al., 2014; Chapman et al., 2015). Evidence from a series of studies from our lab has found that strategy-based reasoning training (described below) improved cognitive functions in both primary and secondary measures across several different populations including individuals with mild cognitive impairment (MCI), traumatic brain injury (TBI), as well as healthy adults and teenagers (Gamino et al., 2010; Anand et al., 2011; Vas et al., 2011, 2016a; Chapman and Mudar, 2014; Chapman et al., 2015, 2016; Mudar et al., 2016). Randomized trials comparing reasoning training to a new learning intervention in adults with TBI in chronic stages post-injury showed significant gains in abstraction, memory, executive functions of working memory and switching, non-verbal reasoning, and daily function (Vas et al., 2011). A larger randomized trial in adults with TBI found similar improvements in measures of executive function, memory and daily function (Vas et al., 2015). In this latter study, the reasoning training was shown to significantly improve psychological health with reduced depression and stress-related symptoms. A comparison of reasoning training versus a new learning intervention in adults with MCI also resulted in significant improvements in executive function and memory measures in the reasoning group (Mudar et al., 2016). A more recent study with healthy adults examined both cognitive and neural changes after reasoning training and found significant improvements in a number of frontally mediated executive functions (Chapman et al., 2015). More notably, this integrative cognitive training induced a number of brain changes at rest, including increased global and regional CBF in the default mode network and central executive network, greater connectivity in these same regions, and increased white matter integrity in the left uncinate (Chapman et al., 2015).

Previous cognitive training approaches with BD have focused largely on targeting specific cognitive processes and measuring improvement through cognitive batteries alone. Additionally, previous training protocols (e.g., cognitive remediation) have tended to require a lengthy time commitment, sometimes up to 24 weeks. In contrast, strategy-based, integrative processes can be trained over a relatively short time-span with training in ways to incorporate strategies into daily life routines. Based on principles of experience-driven plasticity, the likelihood of increased usage throughout daily life may increase chances of achieving spill-over affects into other cognitive domains, maximizing treatment efforts. For instance, in the aforementioned studies which trained reasoning, participants showed improvements in the primary outcome measure, as well as generalized cognitive benefits in other secondary outcome measures of memory and executive functioning skills (Vas et al., 2011, 2015; Chapman et al., 2015).

To date, no known study has investigated the effectiveness of a reasoning training program in individuals with BD. Additionally, of the cognitive trainings completed within the BD population, none have coupled neurocognitive and imaging measures. Therefore, the current phase I pilot trial fills a void by providing preliminary evidence of cognitive and neural benefits from a cognitive training program in individuals with BD. The current study had three major objectives. First, we proposed that a reasoning program, Strategic Memory Advanced Reasoning Training (SMART), would not only improve performance on the primary domain of complex abstraction, but would also show transfer effects to untrained domains of executive function and memory. Our second major goal was to determine whether training induced neuroplasticity changes as measured by resting CBF using pseudo-continuous arterial spin labeling (pCASL) magnetic resonance imaging (MRI). Recent studies demonstrate that CBF is reflective of neuronal health (Chen et al., 2013). Lastly, we were interested in whether the cognitive gains would be linked to specific brain blood flow changes to elucidate possible mechanisms of improvement.

MATERIALS AND METHODS

Participants

A total of 27 adults with a diagnosis of BD I or II between the ages of 21 and 70 (see **Table 1**) participated in this study. Participants were recruited at the University of Texas Southwestern Medical Center, through psychiatrist referral, flyers and website advertising. All participants were native English speakers, had a minimum of high school education, and provided written consent in accordance with the Institutional Review Board (IRB) of our academic institutions: The University of Texas at Dallas and The University of Texas Southwestern Medical Center. Participants underwent a telephone screen with a research clinician, including a brief medical questionnaire covering their history, current medications and any pre-existing conditions. After the participant met the requirements covered by the phone screen, they were asked to complete a neurocognitive testing battery, including the Mini Mental State Exam (MMSE). The inclusion of partially (in addition to fully) remitted individuals served to confirm sufficient sample size and was based on evidence suggesting that residual affective symptoms have no major effects on objective cognitive function (Burdick et al., 2012). If subjects scored $\geq$26 on the MMSE and $\leq$17 on the Hamilton Depression Rating Scale (HAM-D), they were invited to continue with the intervention portion of the study. In addition, participants were administered a standard MRI prescreening form to assess the presence of contraindications for MRI compatibility (e.g., non-removable metal within/on the body, claustrophobia, pregnancy, non-correctable vision problems, head trauma, and CNS disease). Diagnosis of BD and euthymic state was confirmed with collaborating psychiatrist. When the participant was not a patient of the collaborating psychiatrist, written approval was obtained from the treating psychiatrist confirming the following: participant was between ages 21 and 70; participant had a diagnosis of BDI or BDII; participant was in a euthymic, rather than manic or depressive, state; participant had been stable on medications for at least 3 months; and participant was believed to be appropriate for the study. All patients were taking mood stabilizing medications and reported remaining on a consistent dose of medications throughout the study (see **Table 1**).

Procedure

This was a phase I, non-randomized, pilot intervention study examining the neurocognitive and brain changes from a reasoning training program, SMART, in euthymic individuals with BD. Outcome measures were administered at baseline (pre-training, T1) and within 2 weeks after completing the training sessions (post-training, T2). All 27 participants received SMART in small groups of 5–7 people. Groups were led by the same licensed speech-language pathologist. Groups met for 2 h once a week for 4 weeks (total training of 8 h). Groups were formed in order of enrollment and schedule alignment.

Reasoning Training

Strategic Memory Advanced Reasoning Training equips participants with meta-cognitive strategies of Strategic Attention, Integrative Reasoning, and Innovation as a guide for engaging in deeper-level innovative thinking across real-life activities (Chapman and Kirkland, 2014). Strategic Attention targets the ability to filter irrelevant information in order to focus on the important information. Integrative Reasoning targets the ability to abstract meanings from specific key details (be it from a book, medical or legal advice, a movie, conversation, meeting, or other daily interaction), and to interpret within a broader context of world knowledge to create global themes and take away messages that remain relevant to the information or task at hand. Innovation targets perspective-taking, fluency, and novel idea generation in topics or areas of life that have become stagnant.

At the end of each session, participants were given homework assignments that required use of the strategies.

TABLE 1 | Subject characteristics.

Participant demographic	(Mean ± SD)
Total participants (*n*)	**27**
Age at study entry (years)	45.8 ± 12.9
Gender (M/F)	11/16
Education (years)	16.0 ± 1.8
Age of onset (years)	34.0 ± 12.3
Duration of illness (years)	11.8 ± 9.7
Mini Mental State Examination (MMSE)	27.7 ± 1.2
Hamilton Depression Rating Scale (HAMD)	5.9 ± 3.6
Medications (*n*)	**27**
Lithium	8
Anticonvulsant	13
Antipsychotic	17
Antianxiety	4
Antidepressant	7
Benzodiazepines	4

Homework was discussed in the initial portion of the following session, and each participant reported completing the assignments. Exercises utilized a variety of materials, varying in complexity (e.g., articles, artwork, podcasts, current events, TED Talks, etc.) in multiple modalities. Emphasis was put on application of strategies to other contexts (e.g., personal relationships, work environment, and daily responsibilities). The three strategies were presented in sessions one and two, leaving sessions three and four for (1) participant demonstration of how they were incorporating the strategies in their daily lives, (2) participant-generated exercises that required implementation of the strategies (exhibiting further understanding of material), and (3) feedback, questions, and broader conversations focusing on how to practically and independently implement the strategies in daily life, as this was the final goal.

Outcome Measures

Neurocognitive Measures

A battery of neurocognitive measures was administered on a non-training day at two time periods, i.e., baseline/pre-training (T1) and within 2 weeks after training (T2). Cognitive assessment measures were completed in individual, face-to-face testing sessions. All test batteries were pencil and paper measures administered by a trained research clinician (see **Table 2**).

The primary outcome measure of complex abstraction was evaluated using the Test of Strategic Learning (TOSL) (Chapman et al., 2002). Complex abstraction is also referred to as gist reasoning. The TOSL is an assessment that has been previously utilized as a criterion-referenced measure of ability to abstract meaning from complex information in typically developing youth (Chapman et al., 2012; Motes et al., 2014), healthy adults (Anand et al., 2011; Vas et al., 2016a), adults with MCI (Mudar et al., 2016), and adults and youth with TBI (Vas et al., 2011, 2015, 2016a; Cook et al., 2014). Recent evidence supports TOSL as both a sensitive and specific metric of complex abstraction ability (Vas et al., 2016b). Participants read a complex text (approximately 600 words). To evaluate complex abstraction, participants are then instructed to generate a high-level summary of the text. Another subtest of TOSL assesses the ability to recall key facts from the text. The TOSL complex abstraction measure has a manualized objective scoring system where each abstracted idea in the summary receives one point and verbatim or paraphrased ideas do not receive any points, the final score then reflects the total

TABLE 2 | Brief description of outcome variables (scaled scores used if not otherwise specified below).

Variable	Measure	Description
Primary outcome measure		
Complex abstraction	Test of Strategic Learning (TOSL) (Chapman et al., 2002)	Participant synthesizes information into overview. Score: number of abstracted ideas
Secondary outcome measures		
Concept formation	Similarities (Wechsler, 1997a)	Participant explains what pairs of words have in common
Problem solving	D-KEFS Card Sorting Task (Delis et al., 2001)	Participant sorts six cards into two groups of three based on eight different sorting rules
Verbal fluency	Controlled Oral Word Association (COWA) (Benton et al., 1994; Spreen and Strauss, 1998)	Participant says as many words/minute as they can that begin with the given letter
Memory	Logical memory (Wechsler, 1997b)	Participant orally recalls (immediate and delayed) details of a short story read aloud
	Memory for key facts/details (TOSL) (Chapman et al., 2002)	Participant recalls (after probe) specific important facts/details from the text. Score: 0–24
	Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Schmidt, 1996; Spreen and Strauss, 1998)	Participants are given a list of 15 unrelated words repeated over five different trials and are asked to recall. After an interference list is given, the client must again recall the original list of 15 words and then again after 30 min. Score: 0–15 per trial
Working memory	Digits backward (Wechsler, 1997b)	Participant orally recalls number strings in backward order
Inhibition	D-KEFS Color-Word Task, Condition 3 (Delis et al., 2001)	Participant names the color of the ink a work is printed in versus reading the word (color word different than color ink)
Switching	Trails B	Participant alternately connects a set of numbers and letters in ascending alphabetical order
	D-KEFS Color-Word Task, Condition 4 (Delis et al., 2001)	Participant alternates from reading color of printed word and stating ink color of printed word. Score: total time to complete
Daily function	Quality of life in bipolar disorder (Michalak and Murray, 2010)	A 56-item self-report questionnaire on 12 domains of quality of life: Physical, Sleep, Mood, Cognition, Leisure, Social, Spirituality, Finances, Household, Self-esteem, Independence and Identity and two optional domains (Work and Education). Score: 56–280, higher score is associated with higher quality of life

number of accurately abstracted ideas from the text. Different versions of the TOSL were administered at pre- and post-testing.

Secondary outcome measures included tests of executive function (verbal reasoning, problem solving, switching, verbal fluency), memory (including recall for details from TOSL text), complex attention, and quality of life (see **Table 2**). Recall for details from TOSL text yields a maximum possible score of 24. The Quality of Life in Bipolar Disorder (QoL.BD) was created by the Collaborative Research Team to study psychosocial issues in BD (Michalak and Murray, 2010). The QoL.BD scale is the only quality of life questionnaire specifically designed for individuals with BD. The full version has 56 questions within 10 basic domains: physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, and two optional domains (work and education).

MRI Experiment

Magnetic resonance imaging investigations were performed on 12 participants (six males/six females), as the rest of the participants exhibited contraindications for MRI compatibility (non-removable metal within/on the body and claustrophobia). Imaging was performed on a 3 Tesla MR system (Philips Medical System, Best, The Netherlands). A body coil was used for radiofrequency (RF) transmission and an 8-channel head coil with parallel imaging capability was used for signal reception. The MRI scans of participants were performed at rest with their eyes open and on a non-training day. We used a pCASL sequence to measure CBF at rest (Aslan et al., 2010) as well as a high resolution T1 weighted image as an anatomical reference. The details of imaging parameters and their processing techniques are provided below.

Imaging parameters for pCASL experiments were: single-shot gradient-echo EPI, field-of-view (FOV) = 240 × 240, matrix = 80 × 80, voxel size = 3 mm × 3 mm, 27 slices acquired in ascending order, slice thickness = 5 mm, no gap between slices, labeling duration = 1650 ms, time interval between consecutive slice acquisitions = 35.5 ms, TR/TE = 4020/14 ms, SENSE factor 2.5, number of controls/labels = 30 pairs, RF duration = 0.5 ms, pause between RF pulses = 0.5 ms, labeling pulse flip angle = 18°, bandwidth = 2.7 kHz, echo train length = 35, and scan duration 4.5 min. The hypercapnia BOLD imaging parameters were: single shot gradient echo EPI sequence, TR/TE/flip = 2000 ms/25 ms/80°, 43 axial slices, slice thickness = 3.5 mm, FOV = 220 mm × 220 mm, matrix size = 64 × 64 and scan duration = 7 min. The high resolution T1 weighted image parameters were: Magnetization Prepared Rapid Acquisition of Gradient Echo (MPRAGE) sequence, TR/TE = 8.3/3.8 ms, shot interval = 2100 ms, inversion time = 1100 ms, flip angle = 12°, 160 sagittal slices, voxel size = 1 mm × 1 mm × 1 mm, FOV = 256 mm × 256 mm × 160 mm, and duration 4 min.

MRI Analysis

The pCASL MRI data underwent routine processing (Aslan et al., 2010). PCASL image series were realigned to the first volume for motion correction (SPM5's realign function, University College London, UK). All datasets were within the applied motion threshold of 3 mm translation and 3° rotation. An in-house MATLAB (MathWorks, Natick, MA, USA) program was used to calculate the difference between averaged control and label images. The difference image was then corrected for imaging slice delay time to yield CBF-weight image, which was normalized to the brain template from Montreal Neurological Institute (MNI). Lastly, the absolute CBF was estimated in the units of mL blood/min/100 g of brain tissue (Aslan et al., 2010). The absolute whole brain blood flow values were calculated by averaging all the voxels in the absolute CBF (aCBF) map. In voxel based analyses (VBA), the individual aCBF maps were spatially smoothed [with full-width half-maximum (FWHM) of 4 mm] to account for small differences in sulci/gyri location across subjects.

Statistical Analyses

Each neurocognitive measure was considered a dependent variable in a standard linear model. We did not omit subjects whose baseline measures were not paired with their respective post-training measures from lack of follow-up. Thus, the intent-to-treat analyses necessitated the use of a mixed model with time as a within-subject fixed factor and subjects themselves as a random factor. Temporal contrasts, which estimated mean change across the two measurement times, were of primary interest; and all hypotheses were one-sided. That is, we expected only improvements post-training. Given the inclusion of partially (in addition to fully) remitted individuals with BD, we included, in another set of models, the depression measure HAM-D as a covariate with possible interactions temporally. In these models temporal contrasts were conditional on the mean HAM-D estimate across subjects. In addition, we included age as a covariate as well as indicators for the presence or absence of concurrent antipsychotic and anticonvulsive medications to assess any potential effects on the neurocognitive measures. Finally, we applied the Benjamini-Hochberg method to control the false discovery rate (FDR) due to the large number of statistical tests on the neurocognitive battery.

For the voxel-based imaging analyses, each subject had paired measurements pre- and post-training. Thus, voxel level analyses were paired *t*-tests. Statistical inference, however, was at the cluster level using AFNI's *3dclustsim* bootstrap method conditional on a cluster-defining threshold ($p = 0.05$) applied to all voxel-level statistics. At this threshold, contiguous clusters of voxels exceeding 1,449 (11,592 mm^3) in number (volume) were significant at a 0.05 level, corrected for multiple clusters. We also implemented a VBA with age adjusted TOSL scores as a covariate to find potential brain regions where changes in CBF are associated with changes in complex abstraction as measured by TOSL. In this case cluster-level inference proceeded as just described, except that the cluster-defining threshold was $p = 0.005$ and the cluster size threshold for a corrected inference level of 0.01 was 263 voxels (2,104 mm^3).

RESULTS

Neurocognitive Measures

All 27 participants completed 8 h of training. **Table 3** summarizes results for primary and secondary outcomes. Most significant changes include measures of executive function and memory. Executive function measures WAIS Similarities (concept formation) ($p = 0.004$) and DKEFS Card Sorting (problem solving) ($p = 0.001$) improved significantly from pre- to post-training. Immediate memory recall improved on TOSL memory for details ($p = 0.002$). RAVLT scores improved across trials ($p = 0.008$), at a short delay ($p < 0.001$), and at long delay ($p = 0.020$). Our primary measure of complex abstraction did show improvement from pre- to post-training, although not based on the FDR criterion. This is similarly true for Trails B, Digits Backward, and Color-Word (inhibition). When HAM-D was included as a covariate, results were consistent.

MRI Experiment

CBF was measured by pCASL MRI in BD participants' pre- and post-cognitive training. The global CBF did not change significantly from T1 to T2; 51.2 ± 9.8 mL/100 g/min and 52.3 ± 7.8 mL/100 g/min, respectively ($p = 0.40$). The VBA was conducted on relative CBF maps, which included dividing the aCBF maps by the whole brain aCBF. In a prior investigation, we had shown that such technique improves sensitivity of regional differences by reducing physiological variations (Aslan et al., 2010). **Figure 1** shows the VBA results between T1 and T2. The BD group showed a significant increase in blood flow in left IFG after cognitive training (T1 < T2). However, no change was detected in the reverse contrast (T1 > T2). **Table 4** summarizes these findings.

TABLE 3 | Summary of results for each cognitive domain (mean, standard error).

	Pre-training	Post-training	*p*-value
Primary outcome measure			
Complex abstraction			
TOSL	2.35 (0.32)	3.04 (0.32)	0.040
Secondary outcome measures			
Executive function			
WAIS, similarities	12.63 (0.40)	13.61 (0.41)	0.004**
DKEFS card sorting: correct sorts	11.70 (0.42)	13.56 (0.42)	<0.001**
DKEFS card sorting: description	11.74 (0.43)	12.96 (0.43)	0.001**
DKEFS card sorting: recognition	11.56 (0.47)	12.89 (0.47)	0.007**
Trails B	73.44 (5.43)	66.86 (5.48)	0.052
Verbal fluency	11.30 (0.61)	11.82 (0.61)	0.121
Memory			
Logical memory, immediate	13.85 (0.59)	13.30 (0.59)	0.812
Logical memory, delay	11.89 (0.72)	12.26 (0.72)	0.278
TOSL – memory for details	13.26 (1.00)	16.37 (0.98)	0.002**
RAVLT, trial 5	11.96 (0.48)	12.74 (0.48)	0.008**
RAVLT, short delay	9.74 (0.65)	11.44 (0.65)	<0.001**
RAVLT, long delay	9.70 (0.68)	10.93 (0.68)	0.019*
Complex attention			
Digits backward	6.78 (0.36)	7.30 (0.36)	0.039
D-KEFS color-word, condition #3	10.12 (0.54)	11.04 (0.54)	0.023
D-KEFS, color-word, condition #4	11.04 (0.37)	11.46 (0.37)	0.092
Everyday function questionnaires			
Quality of life in bipolar disorder	176.93 (6.90)	183.93 (7.00)	0.095

*FDR = 0.10; **FDR = 0.05.

Neural Correlates of Brain and Cognition

Whole brain voxel-wise correlation analysis between complex abstraction (i.e., TOSL Complex abstraction score and CBF maps, T2–T1) showed significant correlation to right middle frontal CBF; MNI coordinates: [+42 +30 +22], *t*-score of 7.6 and cluster size = 263 voxels (2,104 mm^3, FWE cluster-level $p < 0.01$), shown in **Figure 2**.

DISCUSSION

This feasibility study is the first known attempt to investigate both cognitive (i.e., executive function, memory, complex attention) and brain (i.e., CBF) changes in response to a top–down, strategy-based cognitive training protocol in BD. The novel aspects of this pilot trial are testing a cognitive training protocol (SMART) and brain measurement (CBF) that have previously shown promise in studies focused on harnessing cognitive and neural plasticity. As stated above, SMART teaches top–down, metacognitive strategies that can be utilized in everyday life and its efficacy is supported by prior evidence of improved executive function and frontoparietal networks in other clinical and healthy populations (Chapman et al., 2015, 2016; Vas et al., 2015; Mudar et al., 2016). Previous neurobehavioral interventions in BD have focused largely on improving the psychological health with only more recent focus on targeting the cognitive deficits that have now been well-documented (Deckersbach et al., 2010; Preiss et al., 2013; Torrent et al., 2013; Demant et al., 2015). Additionally, recent technological advancements in resting state MRI allow measurement of neuroplasticity changes with CBF, which is beginning to show promise as one potential objective neural marker of enhanced brain health. This potential measurement of neuroplasticity change is derived from a well-accepted coupling between healthy neural activity and cerebrovascular flow (Raichle and Gusnard, 2002; Chapman et al., 2016), as well as accumulating evidence that different forms of interventions show increased CBF with concomitant improvement in cognitive functions (Takeuchi et al., 2013; Chapman and Mudar, 2014; Chapman et al., 2015, 2016; Vas et al., 2016a).

Three major findings emerged from this pilot study. First, we found that a strategy-based reasoning training, delivered over 4 weeks with 2 h each week for a total of 8 h, improved complex abstraction abilities in adults with BD. Moreover, the training showed generalized benefits to other cognitive domains that were not specifically trained, including specific executive functions (i.e., concept abstraction and problem solving) and memory

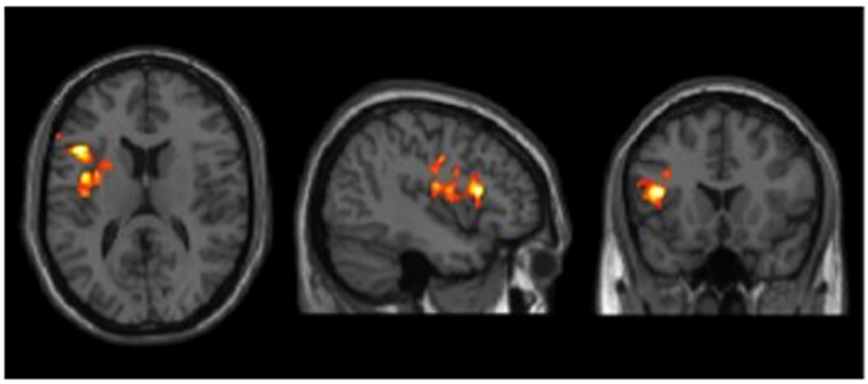

FIGURE 1 | Results of cerebral blood flow (CBF) voxel based comparison superimposed on T1 image. Bipolar disorder (BD) participants showed a CBF increase in left inferior frontal gyrus from T1 to T2 after cognitive training, $p < 0.05$ (FWE cluster corrected) and $k \geq 11{,}592$ mm^3.

TABLE 4 | Cerebral blood flow (CBF) regions that showed significant blood flow change at rest in bipolar disorder (BD) group from T1 to T2.

			MNI			
Brain regions	**BA**	**Cluster size (mm^3)**	***X***	***Y***	***Z***	***T*-value**
Pre-Training < Post-Training						
Left Inferior Oper. Frontal G	13/45/6/44	11,752	−42	18	14	6.79
Pre-Training > Post-Training						
None						

FWE cluster level, corrected $p < 0.05$, voxel threshold at $p = 0.05$ and $K = 11{,}592$ mm^3.

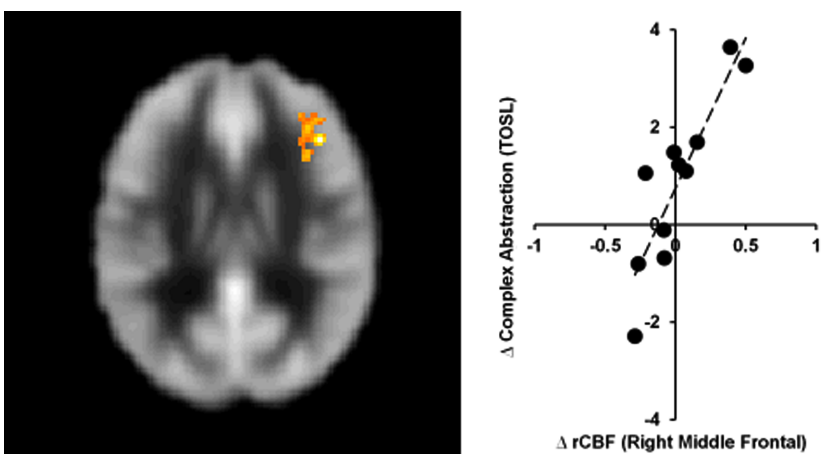

FIGURE 2 | Bipolar disorder group showed significant association between gains in regional CBF and behavioral measures. The BD group's TOSL complex abstraction score difference showed significant association to right middle frontal CBF increase at T2, cluster-level $p < 0.01$ (FWE corrected).

(word lists at immediate and delayed periods and details from complex information). Secondly, we found significant pre to post increases in CBF in the left prefrontal cortex, namely in the left inferior frontal gyrus (LIFG), a region of the brain associated with semantic and cognitive control processes (Poldrack et al., 1999; Gold et al., 2006; Badre and Wagner, 2007; Danker et al., 2008; Race et al., 2009). Third, we found a positive correlation between enhanced cognition (complex abstraction) and increased resting CBF in the right prefrontal cortex, supporting the potential for the training to positively impact both brain and cognition; in other words, enhance brain health.

Our findings of improved executive functions in BD with SMART concur with recent evidence from other trainings that impairments in executive function in BD can be mitigated with cognitive training (Deckersbach et al., 2010; Preiss et al., 2013). The trainings in these two prior studies trained a broad-base of specific processes whereas our training taught strategies to deal with complex information and contexts encountered in

everyday life. Additionally, we found significant improvement on memory measures, a cognitive domain which has not previously shown to be enhanced in other cognitive training studies with BD. These findings support SMART training as an integrative, top–down process that promotes not only synthesizing and abstraction of information, but can also potentially promote deeper encoding and recall of information. Current results add to prior evidence that cognitive training of higher-order integrative functions, which equip individuals with strategies to employ throughout their daily routine after training has ended, could be a beneficial intervention, when used to complement standard of care therapeutic approaches in BD.

Since both our training and the Preiss et al. (2013) study took only 8 h of training, we propose that short-term cognitive interventions may be worth the cost in terms of time and money since they appear to provide benefits in mitigating cognitive deficits in BD. Moreover, the present results add to the emerging evidence that neurotherapeutic management and overall life functionality in BD may be improved when the cognitive deficits are addressed along with the psychiatric symptoms of depression (Deckersbach et al., 2010). The current results suggest the degree of depressive symptoms was not a contributing factor that impacted response to cognitive training, a promising finding which suggests these psychiatric problems are not necessarily a limiting factor to treatment benefit. Treatment of psychiatric disorders, e.g., BD, and other brain disorders has far too long been siloed with sole focus on only one domain of brain health rather than taking into account other aspects of brain health, both cognitive and psychological health. For example, the psychiatric symptoms in BD tend to be the sole focus of management without addressing the co-occurring cognitive deficits. In a contrasting focus, in acquired brain injury the key focus has been on remediating executive functions without concern for the co-morbid psychiatric problems, such as depression and anxiety which are being identified (Didehbani et al., 2013; Max et al., 2015). The potential for cognitive training to show spillover effects to improving psychological health benefits is intriguing. In a previous study, we found that SMART training in adults with TBI showed not only cognitive gains but also psychological benefits that were manifested by a significant reduction of depressive and stress-related symptoms that continued to improve 3 months after the training ceased (Vas et al., 2016a). Unfortunately, we failed to measure post-treatment psychological health in BD in the present study. Nonetheless, Deckersbach et al. (2010) showed that cognitive training was associated with a decrease in residual depressive symptoms as well-increased occupational and overall psychosocial functioning immediately and at 3 month follow up.

In addition to improvement on neurocognitive measures, imaging results showed increased regional brain blood flow in the left prefrontal cortex. There is considerable controversy as to whether increased CBF is associated with improved brain function (Sojkova et al., 2008) or compensatory reaction. Much of the controversy arises in activation studies, but less so in resting state CBF studies. For example, activation studies have measured both increases and decreases in BOLD signal during mental activation tasks. What is important to note, however, is that this change is a transient effect and is typically restored to baseline level when the brain returns to resting state (Raichle and Gusnard, 2002). Therefore, as a tightly regulated system, resting CBF is remarkably consistent and an important biomarker (Raichle and Gusnard, 2002). Additionally, results from a growing number of studies reveal that resting state CBF may represent a promising neural marker of brain response to distinct interventions across clinical populations (Mozolic et al., 2010; Vas et al., 2015). These studies identify a correlation between increased CBF and improved cognitive function with healthy agers and those with brain injury (Takeuchi et al., 2013; Chapman et al., 2015, 2016; Vas et al., 2015). We propose that the increased resting CBF in the present study of individuals with BD reflects a similar improvement. Specifically within the frontal lobe, we found a significant increase in resting CBF in the LIFG (which showed a significant gain from pre- to post-training). Other researchers have supported the pivotal role of the LIFG as being associated with cognitive control processes, such as executive function (Poldrack et al., 1999; Gold et al., 2006; Badre and Wagner, 2007; Danker et al., 2008; Race et al., 2009). What is intriguing and perhaps strengthens the present results, is that we also previously reported increased resting CBF in the LIFG at post SMART training in other populations (Chapman et al., 2015; Vas et al., 2015).

Thirdly, we found a significant association between increased CBF in the right middle frontal gyrus (MFG) and improved complex abstraction. We speculate that the reasoning training engaged cognitive control to facilitate processing of complex information that also involved fine-tuning of attentional systems to inhibit less important information with concomitant improvement in prefrontal cortex (Chapman et al., 2016). Supporting this plausible explanation, Corbetta et al. (2008) have shown the right MFG to be a potential modulator between attention networks. Additionally, the right frontal cortex has previously been associated with increased CBF being linked to higher complex abstraction performance (Chiu Wong et al., 2006).

Whereas the current results require further examination in larger clinical trials, the capacity to induce increased resting CBF in the prefrontal cortex of individuals with BD as a result of integrative cognitive training could have beneficial clinical implications. This is the first known study to investigate brain changes in response to cognitive training in BD with findings suggesting improvement to brain areas that might be compromised by the disease, such as the prefrontal cortex (Blumberg et al., 2003; Phillips et al., 2003, 2008; Kronhaus et al., 2006; Green et al., 2007). In sum, we propose that the increased health of the frontal regions, as manifested by elevated CBF, could be a result of experience-driven neural plasticity where the concerted cognitive effort recruited and improved the health of this neural system.

Limitations and Future Directions

This study has a number of strengths, which include utilization of brain and neurocognitive outcome measures, as well as implementation of a novel cognitive training intervention for individuals with BD. We also note a number of limitations which

make us interpret our findings cautiously. The major limitations include the lack of either a waitlist or active control group and the fact that the same clinician trained and tested participants. With regard to the first limitation of no control group, we cannot rule out the possibility of practice effects; however, we do not feel that practice effects account for the gains across measures, especially given the convergence of gains in cognition and increased CBF. Additionally, in prior studies testing efficacy of SMART, which included active control or wait-list control groups, we found similar executive function and neural benefits from the reasoning training as compared to the control groups. Specifically, studies with traumatic brain injury populations demonstrated similar gains in areas of complex abstraction, executive function, and memory after training; whereas the control group exhibited no significant gains in any cognitive domains (Vas et al., 2011; Cook et al., 2014). Studies examining SMART training with healthy individuals, both adolescent and adult, resulted in significantly improved ability in measures of executive function including complex abstraction and memory, while the control group showed no significant gains in any cognitive domains (Gamino et al., 2010; Chapman et al., 2015). Similarly, in a population at-risk for Alzheimer's, Mudar et al. (2013) found significant improvements following the SMART protocol on measures of abstraction, executive function, and memory relative to the active control group, which showed no such significant gains except for the D-KEFS sorting test. Regarding the second potential limitation of clinician bias, two clinicians, who were unaware of time of testing (i.e., pre or post) scored the key measures independently to minimize experimenter bias. Moreover, participants' pre- to post-responses were not paired for scoring so that no comparison between pre and post response could bias change scores. We failed to find significant differences between scores of the two raters. Alternate versions of primary and secondary measures were used, when available, at pre- and post-testing to also help reduce practice effect. We recognize that future studies should include a control group as well as blind the examiners to group membership. Nonetheless, we do not feel that these two factors fully explain the current findings and believe the current results offer a promising pattern of findings that motivate a more in-depth trial.

Another potential weakness, but also strength, is the limited range of depressive symptoms. As our participants had relatively low depression scores, it would be interesting to consider whether patients with greater levels of depressive symptoms would show different degrees of benefit, perhaps more or perhaps less. The fact that the degree of affective symptoms did not affect results leaves the question open as to whether those with more serious levels of symptomatology might still benefit. A recent review concluded that cognitive effects of lithium, anticonvulsants, and antipsychotics on cognition in BD are still unknown, primarily due to flawed research methodology, small sample sizes, and inconsistent findings (Vreeker et al., 2015). In this current study, however, we did assess the potential effects of anticonvulsants and antipsychotics. Neither medication type nor its interaction with time were significantly different for any behavioral measure. With a larger sample size, we could also more clearly examine effects of medications, such as anti-psychotics and mood stabilizers, as well as dosage effects. We find the strength of the current results encouraging for conducting a larger trial to confirm these findings and consider other questions such as treatment earlier in the disease course, perhaps after the first episode of depression. Additional weaknesses are the relatively small sample size, a lack of post-testing in psychological health, testing at extended periods post-treatment to evaluate whether the gains persisted and the failure to consider occupational functionality.

The cognitive gains from the current study replicate previous findings of training-specific gains, as well as generalized improvement in cognitive skills in various clinical populations that underwent reasoning training (Anand et al., 2011; Vas et al., 2011, 2015; Mudar et al., 2016). We propose that these preliminary data motivate a larger, randomized study. A larger sample size would also allow better assessment as to what, if any, distinct effect depressive symptoms had regarding training benefits. Future investigations should also include indicators of level of engagement and long-term follow-up assessments (e.g., 6 and 12 months post) to evaluate maintenance of gains, as well as earlier in the disease course.

CONCLUSION

The impact of cognitive training protocols is a particularly important line of research in BD. The potential to strengthen mental capabilities, and executive functions, in particular, may be a tangible path to motivate a productive life style course in populations with psychiatric disorders where the cognitive sequela has been relatively unexplored. Strengthening neural circuits through cognitive training in individuals with psychiatric disease may provide one promising adjuvant to the pharma-interventions to supplement individuals' capacity with psychiatric disease to achieve higher levels of success in personal and occupational goals, as has been suggested by Fisher et al. (2009).

AUTHOR CONTRIBUTION

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

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REFERENCES

Anand, R., Chapman, S. B., Rackley, A., Keebler, M., Zientz, J., and Hart, J. (2011). Gist reasoning training in cognitively normal seniors. *Int. J. Geriatr. Psychiatry* 26, 961–968. doi: 10.1002/gps.2633

Aslan, S., Xu, F., Wang, P. L., Uh, J., Yezhuvath, U. S., van Osch, M., et al. (2010). Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. *Magn. Reson. Med.* 63, 765–771. doi: 10.1002/mrm.22245

Badre, D., and Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45, 2883–2901. doi: 10.1016/j.neuropsychologia.2007.06.015

Benabarre, A., Vieta, E., Martínez-Arán, A., Garcia-Garcia, M., Martín, F., Lomeña, F., et al. (2005). Neuropsychological disturbances and cerebral blood flow in bipolar disorder. *Aust. N. Z. J. Psychiatry* 39, 227–234. doi: 10.1080/j.1440-1614.2004.01558.x

Benton, A. L., Hamsher, K. D., and Sivan, A. B. (1994). *Multilingual Aphasia Examination: Manual of Instructions*. Iowa City, IA: AJA Associates Inc.

Blumberg, H. P., Leung, H.-C., Skudlarski, P., Lacadie, C. M., Fredericks, C. A., Harris, B. C., et al. (2003). A functional magnetic resonance imaging study of bipolar disorder: state-and trait-related dysfunction in ventral prefrontal cortices. *Arch. Gen. Psychiatry* 60, 601–609. doi: 10.1001/archpsyc.60.6.601

Burdick, K. E., Braga, R. J., Nnadi, C. U., Shaya, Y., Stearns, W. H., and Malhotra, A. K. (2012). Placebo-controlled adjunctive trial of pramipexole in patients with bipolar disorder: targeting cognitive dysfunction. *J. Clin. Psychiatry* 73, 103–112. doi: 10.4088/JCP.11m07299

Chapman, S. B., Aslan, S., Spence, J., Keebler, M. W., DeFina, L. F., Didehbani, N., et al. (2016). Distinct brain and behavioral benefits from cognitive versus physical training: a randomized trial in aging adults. *Front. Hum. Neurosci.* 10:338. doi: 10.3389/fnhum.2016.00338

Chapman, S. B., Aslan, S., Spence, J. S., Hart, J. J. Jr, Bartz, E. K., Didehbani, N., et al. (2015). Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. *Cereb. Cortex* 25, 396–405. doi: 10.1093/cercor/bht234

Chapman, S. B., Gamino, J. F., and Mudar, R. A. (2012). "Higher-order strategic gist reasoning in adolescence," in *The Adolescent Brain: Learning, Reasoning, and Decison Making*, eds V. Reyna, S. B. Chapman, M. R. Dougherty, and J. Confrey (Washington, DC: American Psychological Association), 123–151.

Chapman, S. B., and Kirkland, S. (2014). *Make Your Brain Smarter: Increase Your Brain's Creativity, Energy, and Focus*. New York City, NY: Simon and Schuster.

Chapman, S. B., and Mudar, R. A. (2014). Enhancement of cognitive and neural functions through complex reasoning training: evidence from normal and clinical populations. *Front. Syst. Neurosci.* 8:69. doi: 10.3389/fnsys.2014.00069

Chapman, S. B., Zientz, J., Weiner, M., Rosenberg, R., Frawley, W., and Burns, M. H. (2002). Discourse changes in early Alzheimer disease, mild cognitive impairment, and normal aging. *Alzheimer Dis. Assoc. Disord.* 16, 177–186. doi: 10.1097/00002093-200207000-00008

Chen, C. H., Suckling, J., Lennox, B. R., Ooi, C., and Bullmore, E. T. (2011). A quantitative meta-analysis of fMRI studies in bipolar disorder. *Bipolar Disord.* 13, 1–15. doi: 10.1111/j.1399-5618.2011.00893.x

Chen, J. J., Rosas, H. D., and Salat, D. H. (2013). The relationship between cortical blood flow and sub-cortical white-matter health across the adult age span. *PLoS ONE* 8:e56733. doi: 10.1371/journal.pone.0056733

Chiu Wong, S. B., Chapman, S. B., Cook, L. G., Anand, R., Gamino, J. F., and Devous, M. D. Sr. (2006). A SPECT study of language and brain reorganization three years after pediatric brain injury. *Prog. Brain Res.* 157, 173–394. doi: 10.1016/S0079-6123(06)57011-6

Cook, L. G., Chapman, S. B., Elliott, A. C., Evenson, N. N., and Vinton, K. (2014). Cognitive gains from gist reasoning training in adolescents with chronic-stage traumatic brain injury. *Front. Neurol.* 5:87. doi: 10.3389/fneur.2014.00087

Corbetta, M., Patel, G., and Shulman, L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron* 58, 306–324. doi: 10.1016/j.neuron.2008.04.017

Danker, J. F., Gunn, P., and Anderson, J. R. (2008). A rational account of memory predicts left prefrontal activation during controlled retrieval. *Cereb. Cortex* 18, 2674–2685. doi: 10.1093/cercor/bhn027

Deckersbach, T., Nierenberg, A. A., Kessler, R., Lund, H. G., Ametrano, R. M., Sachs, G., et al. (2010). RESEARCH: cognitive rehabilitation for bipolar disorder: an open trial for employed patients with residual depressive symptoms. *CNS Neurosci. Ther.* 16, 298–307. doi: 10.1111/j.1755-5949.2009.00110.x

Delis, D. C., Kaplan, E., and Kramer, J. H. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: Psychological Corporation.

Demant, K. M., Vinberg, M., Kessing, L. V., and Miskowiak, K. W. (2015). Effects of short-term cognitive remediation on cognitive dysfunction in partially or fully remitted individuals with bipolar disorder: results of a randomised controlled trial. *PLoS ONE* 10:e0127955. doi: 10.1371/journal.pone.0127955

Didehbani, N., Cullum, C. M., Mansinghani, S., Conover, H., and Hart, J. (2013). Depressive symptoms and concussions in aging retired NFL players. *Arch. Clin. Neuropsychol.* 28, 418–424. doi: 10.1093/arclin/act028

Fisher, M., Holland, C., Merzenich, M. M., and Vinogradov, S. (2009). Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *Am. J. Psychiatry* 166, 805–811. doi: 10.1176/appi.ajp.2009.08050757

Gamino, J. F., Chapman, S. B., Hull, E. L., and Lyon, G. R. (2010). Effects of higher-order cognitive strategy training on gist-reasoning and fact-learning in adolescents. *Front. Psychol.* 1:188. doi: 10.3389/fpsyg.2010.00188

Gold, B. T., Balota, D. A., Jones, S. J., Powell, D. K., Smith, C. D., and Andersen, A. H. (2006). Dissociation of automatic and strategic lexical-semantics: functional magnetic resonance imaging evidence for differing roles of multiple frontotemporal regions. *J. Neurosci.* 26, 6523–6532. doi: 10.1523/jneurosci.0808-06.2006

Green, M. J., Cahill, C. M., and Malhi, G. S. (2007). The cognitive and neurophysiological basis of emotion dysregulation in bipolar disorder. *J. Affect. Disord.* 103, 29–42. doi: 10.1016/j.jad.2007.01.024

Kronhaus, D. M., Lawrence, N. S., Williams, A. M., Frangou, S., Brammer, M. J., Williams, S. C. R., et al. (2006). Stroop performance in bipolar disorder: further evidence for abnormalities in the ventral prefrontal cortex. *Bipolar Disord.* 8, 28–39. doi: 10.1111/j.1399-5618.2006.00282.x

Martinez-Aran, A., Vieta, E., Colom, F., Torrent, C., Sanchez-Moreno, J., Reinares, M., et al. (2004). Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. *Bipolar Disord.* 6, 224–232. doi: 10.1111/j.1399-5618.2004.00111.x

Max, J. E., Lopez, A., Wilde, E. A., Bigler, E. D., Schachar, R. J., Saunders, A., et al. (2015). Anxiety disorders in children and adolescents in the second six months after traumatic brain injury. *J. Pediatr. Rehabil. Med.* 8, 345–355. doi: 10.3233/PRM-150352

Michalak, E. E., and Murray, G. (2010). Development of the QoL. BD: a disorder-specific scale to assess quality of life in bipolar disorder. *Bipolar Disord.* 12, 727–740. doi: 10.1111/j.1399-5618.2010.00865.x

Motes, M. A., Gamino, J. F., Chapman, S. B., Rao, N. K., Maguire, M. J., Brier, M. R., et al. (2014). Inhibitory control gains from higher-order cognitive strategy training. *Brain Cogn.* 84, 44–62. doi: 10.1016/j.bandc.2013.10.007

Mozolic, J. L., Hayaska, S., and Laurienti, P. J. (2010). A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Front. Hum. Neurosci.* 4:16. doi: 10.3389/neuro.09.016.2010

Mudar, R., Chiang, H.-S., Eroh, J., Rackley, A., Venza, E., Martin-Cook, K., et al. (2013). "Benefits of cognitive training in individuals with mild cognitive impairment," in *Poster Presentation – Cognitive Neuroscience Society Annual Meeting*, San Francisco, CA.

Mudar, R. A., Chapman, S. B., Rackley, A., Eroh, J., Chiang, H. S., Perez, A., et al. (2016). Enhancing latent cognitive capacity in mild cognitive impairment with gist reasoning training: a pilot study. *Int. J. Geriatr. Psychiatry* doi: 10.1002/gps.4492 [Epub ahead of print].

O'Connell, R. A., Van Heertum, R. L., Luck, D., Yudd, A. P., Cueva, J. E., Billick, S. B., et al. (1995). Single-photon emission computed tomography of

the brain in acute mania and schizophrenia. *J. Neuroimag.* 5, 101–104. doi: 10.1111/jon199552101

Phillips, M. L., Drevets, W. C., Rauch, S. L., and Lane, R. (2003). Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol. Psychiatry* 54, 504–514. doi: 10.1016/S0006-3223(03)00168-9

Phillips, M. L., Ladouceur, C. D., and Drevets, W. C. (2008). A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol. Psychiatry* 13, 833–857. doi: 10.1038/mp.2008.65

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. E. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10, 15–35. doi: 10.1006/nimg.1999.0441

Preiss, M., Shatil, E., Cermakova, R., Cimermanova, D., and Ram, I. (2013). Personalized cognitive training in unipolar and bipolar disorder: a study of cognitive functioning. *Front. Hum. Neurosci.* 7:108. doi: 10.3389/fnhum.2013.00108

Quraishi, S., and Frangou, S. (2002). Neuropsychology of bipolar disorder: a review. *J. Affect. Disord.* 72, 209–226. doi: 10.1016/S0165-0327(02)00091-5

Race, E. A., Shanker, S., and Wagner, A. D. (2009). Neural priming in human frontal cortex: multiple forms of learning reduce demands on the prefrontal executive system. *J. Cogn. Neurosci.* 21, 1766–1781. doi: 10.1162/jocn.2009.21132

Raichle, M. E., and Gusnard, D. A. (2002). Appraising the brain's energy budget. *Proc. Natl. Acad. Sci. U.S.A.* 99, 10237–10239. doi: 10.1073/pnas.172399499

Rey, A. (1964). *L'examen Clinique en Psychologie [The clinical psychological examination]*. Paris: Presses Universitaires de France.

Robinson, L. J., and Ferrier, I. N. (2006). Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disord.* 8, 103–116. doi: 10.1111/j.1399-5618.2006.00277.x

Schmidt, M. (1996). *Rey Auditory Verbal Learning Test: A Handbook*. Los Angeles, CA: Western Psychological Services.

Sojkova, J., Beason-Held, L., Zhou, Y., An, Y., Kraut, M. A., Ye, W., et al. (2008). Longitudinal cerebral blood flow and amyloid deposition: an emerging pattern? *J. Nucl. Med.* 49, 1465–1471. doi: 10.2967/jnumed.108.051946

Spreen, O., and Strauss, E. (1998). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York, NY: Oxford University Press.

Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., et al. (2013). Effects of working memory training on functional connectivity and cerebral blood flow during rest. *Cortex* 49, 2106–2125. doi: 10.1016/j.cortex.2012.09.007

Torrent, C., del Mar Bonnin, C., Martínez-Arán, A., Valle, J., Amann, B. L., González-Pinto, A., et al. (2013). Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *Am. J. Psychiatry* 170, 852–859. doi: 10.1176/appi.ajp.2012.12070971

van Gorp, W. G., Altshuler, L., Theberge, D. C., Wilkins, J., and Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. *A preliminary study. Arch. Gen. Psychiatry* 55, 41–46. doi: 10.1001/archpsyc.55.1.41

Vas, A., Chapman, S., Aslan, S., Spence, J., Keebler, M., Rodriguez-Larrain, G., et al. (2016a). Reasoning training in veteran and civilian traumatic brain injury with persistent mild impairment. *Neuropsychol. Rehabil.* 26, 502–531. doi: 10.1080/09602011.2015.1044013

Vas, A., Spence, J., Eschler, B., and Chapman, S. (2016b). Sensitivity and specificity of abstraction using gist reasoning measure in adults with traumatic brain injury. *J. Appl. Biobehav. Res.*

Vas, A. K., Chapman, S. B., and Cook, L. G. (2015). Language impairments in traumatic brain injury: a window into complex cognitive performance. *Handb. Clin. Neurol.* 128, 497–510. doi: 10.1016/b978-0-444-63521-1.00031-5

Vas, A. K., Chapman, S. B., Cook, L. G., Elliott, A. C., and Keebler, M. (2011). Higher-order reasoning training years after traumatic brain injury in adults. *J. Head Trauma Rehabil.* 26, 224–239. doi: 10.1097/HTR.0b013e318218dd3d

Vreeker, A., van Bergen, A. H., and Kahn, R. S. (2015). Cognitive enhancing agents in schizophrenia, and bipolar disorder. *Eur. Neuropsychopharmacol.* 25, 969–1002. doi: 10.1016/j.euroneuro.2015.04.014

Wechsler, D. (1997a). *Manual for the Wechsler Adult Intelligence Scale-III*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale (WMS-III)*. San Antonio, TX: Psychological Corporation.

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