RETURNING TO MECHANISMS IN PSYCHOLOGICAL THERAPIES: UNDERSTAND THE ENGINE BEFORE STEAMING IN

EDITED BY: Warren Mansell, David E. Linden, Veena Kumari and Liam Mason

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RETURNING TO MECHANISMS IN PSYCHOLOGICAL THERAPIES: UNDERSTAND THE ENGINE BEFORE STEAMING IN

Topic Editors:
Warren Mansell, The University of Manchester, United Kingdom
David E. Linden, Maastricht University Medical Centre, Netherlands
Veena Kumari, Brunel University London, United Kingdom
Liam Mason, University College London, United Kingdom

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EDITORIAL
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Editorial: Returning to Mechanisms in Psychological Therapies: Understand the Engine Before Steaming in

Liam Mason[1,2,3]*, *Warren Mansell*[4], *David E. J. Linden*[5] *and Veena Kumari*[6]

[1] Max Planck University College London Centre for Computational Psychiatry and Ageing Research, University College London, London, United Kingdom, [2] Wellcome Centre for Human Neuroimaging, University College London, London, United Kingdom, [3] Research Department of Clinical, Educational and Health Psychology, University College London, London, United Kingdom, [4] Division of Psychology and Mental Health, CeNTrUM Centre for New Treatments and Understanding in Mental Health, Manchester Academic Health Science Centre, Faculty of Biology, Medicine and Health, School of Health Sciences, University of Manchester, Manchester, United Kingdom, [5] Faculty of Health, Medicine and Life Sciences, School for Mental Health and Neuroscience, Maastricht University, Maastricht, Netherlands, [6] Centre for Cognitive Neuroscience, College of Health, Medicine and Life Sciences, Brunel University London, Uxbridge, United Kingdom

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Editorial on the Research Topic

Returning to Mechanisms in Psychological Therapies: Understand the Engine Before Steaming in

Many pivotal techniques from evidence-based psychological interventions for other disorders grew from basic research into mechanistic processes. Yet the past few decades have seen the field of psychological interventions drift away from its scientific roots. This year, the Lancet commission for improving psychological treatments (1) urged greater synergy between basic and clinical research, and integration with technology and physiological measures. This special section focuses on bringing a mechanistic focus to psychological therapies and showcases some of the most recent advances in understanding the mechanisms of psychological therapy across ten important theoretical and empirical contributions in the field.

Setting the scene, Carey et al. attempt a review of potential functional mechanisms (i.e., mechanisms that "express plausible actions consistent with known biological processes") underlying positive outcomes in psychological therapy. Their findings are thought provoking in showing a lack of empirical research on this topic and present a strong case for clinicians and researchers to work together and link psychological intervention practises to scientific theories capable of integrating functional mechanisms and biological processes if we are to advance meaningfully in this area. Next, Watkins and Newbold outline how trial designs can be exploited to better understand how psychological interventions exert their therapeutic effects. Moving beyond the identification of statistical mediation effects, they detail The Multiphase Optimality Strategy; a sophisticated way of assessing the active ingredients of a multi-component psychological intervention by blending different elements within a factorial design.

Going beyond studying the effects of experimental manipulations, Mansell and Huddy build on the view that the most robust test for a psychological mechanism arises from constructing a neurally plausible functional model of the mechanism using a computational framework. They focus specifically on perceptual control theory which provides a mathematical specification of principles that may be fundamental to mental health—namely control, conflict and reorganisation. Their article provides a review of existing studies and describes

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Edited by:
Asle Hoffart, Modum Bad Psychiatric Center, Norway

Reviewed by:
Henrik Nordahl, Norwegian University of Science and Technology, Norway

***Correspondence:**
Liam Mason
l.mason@ucl.ac.uk

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the methodology of this approach. Nair et al. also advocate a computational approach, and outline how computational psychiatry models rooted within a reinforcement learning framework could be clinically applied to understanding mechanisms in mood disorders, and to make existing therapies more mechanism-focused. They focus on making expectation and reward prediction errors more explicit in behavioural activation and behavioural experiments, and discuss parameters from computational models as useful "read-outs" for evaluating progress in psychological therapy.

Shifting gears to empirical investigation of mechanisms, Di Simplicio et al. examine mental imagery as a potential endophenotype for affective disorder; that is, whether imagery differences are a manifestation of genetic contributions that precede diagnosis. They tested whether imagery differences are present in a group at elevated genetic risk for affective disorders, as well as in a group who had been diagnosed with an affective disorder but were out of episode. They did not find support for an endophenotype account; imagery abnormalities were only present in those who had been diagnosed with an affective disorder, suggesting that they are markers of established affective disorder. The authors argue that this mechanism likely increases vulnerability to future relapse and therefore represents an important target for personalised imagery-based intervention.

Moving from behavioural measures to physiological measures, Skottnik and Linden outline how advances in real-time neurofeedback from functional MRI can be used to advance our understanding of the neural mechanisms of imagery interventions and potentially increase their effectiveness. Like Di Simplicio et al. (2), they stress the role of mental imagery in current psychotherapeutic approaches, particularly in reducing negative biases in depression and for imaginal exposure in anxiety disorders. They detail how insights into the neural mechanisms of mental imagery can give rise to new neuromodulation approaches like neurofeedback, a self-regulation training of brain activity. They argue that a systematic combination with psychotherapeutic techniques will be crucial for the translation of neurofeedback into a clinical tool.

Riedl et al. (3) also harness neurobiological measurements, using functional MRI to investigate the therapeutic mechanism of activation of a novel training intervention for psychosis. Their trial has a particularly innovative combination of outcome measures, covering cognitive performance (e.g., working memory), social skills (e.g., self- and informant assessed communicative abilities) and neural measures (fMRI acquired during the presentation of audiovisual communication signals). It is thus paradigmatic for the topic of this volume, with its combination of clinical and mechanistic evaluation of cognitive-behavioural interventions.

Griffith and Saunders outline the utility of smartphone-based assessments as an objective measure of mood. This technology provides one excellent avenue for testing the computational approaches advocated within this special issue. The article provides an up-to-date overview of this burgeoning area of research, explaining the advantages of this technology for frequent, ecologically valid assessment of data, some of which can be recorded continuously with no effort from the participants. They also clarify the challenges and controversies of this methodology, including issues regarding data security and participant preoccupation with the monitoring technology. A potential direction for physiological and digital assessment is its application to chronic physical illnesses; the first step being to identify the underlying mechanism involved in distress regarding the illness. Khatibi et al. report a psychometric evaluation of a Fear of Relapse scale in patients with Multiple Sclerosis, finding evidence for its distinctiveness, reliability and validity.

Finally, moving to a real example of treatment innovation Hirsch et al. describe how theory-driven empirical research can be used to make cognitive-behavioural interventions for generalised anxiety disorder more mechanism-focused. They isolate worry as an overarching process at the core, and detail a modified 12-session intervention; noteworthy as this is briefer and therefore potentially more efficient than standard interventions. They indeed report reductions in worry and general anxiety with large effects ($d = 0.90–2.54$) that exceed standard interventions, with the next step being to quantify how much of the added effectiveness is due to this modified approach.

Taken together, the articles in this collection crystallise a scientific approach that advocates precise specification, modelling and measurement of putative mechanisms of psychological therapies, that directly translates to the development of advanced, efficient and targeted interventions. The role of the human therapist is likely to become increasingly scrutinised as these developments in therapy unfold. Are they an expert who applies a well-honed technique to target the mechanism within a compliant client—or a facilitator who uses their understanding of mechanism to flexibly enable active, client-led change?

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

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REVIEW
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Mental Imagery and Brain Regulation—New Links Between Psychotherapy and Neuroscience

*Leon Skottnik and David E. J. Linden**

School for Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands

Mental imagery is a promising tool and mechanism of psychological interventions, particularly for mood and anxiety disorders. In parallel developments, neuromodulation techniques have shown promise as add-on therapies in psychiatry, particularly non-invasive brain stimulation for depression. However, these techniques have not yet been combined in a systematic manner. One novel technology that may be able to achieve this is neurofeedback, which entails the self-regulation of activation in specific brain areas or networks (or the self-modulation of distributed activation patterns) by the patients themselves, through real-time feedback of brain activation (for example, from functional magnetic resonance imaging). One of the key mechanisms by which patients learn such self-regulation is mental imagery. Here, we will first review the main mental imagery approaches in psychotherapy and the implicated brain networks. We will then discuss how these networks can be targeted with neuromodulation (neurofeedback or non-invasive or invasive brain stimulation). We will review the clinical evidence for neurofeedback and discuss possible ways of enhancing it through systematic combination with psychological interventions, with a focus on depression, anxiety disorders, and addiction. The overarching aim of this perspective paper will be to open a debate on new ways of developing neuropsychotherapies.

Keywords: mental imagery, emotion-regulation, psychotherapy, neuromodulation, neurofeedback, real-time fMRI, brain stimulation

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Edited by:
Gary P. Brown, University of London, United Kingdom

Reviewed by:
Tibor Auer, Royal Holloway, University of London, United Kingdom
Kirsten Nele Emmert, Université de Genève, Switzerland

***Correspondence:**
David Linden
david.linden@maastrichtuniversity.nl

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INTRODUCTION

The neural mechanisms of psychotherapy have been investigated with methods of functional imaging for over 20 years (1–4). This line of investigation has fascinated psychotherapists and neuroscientists alike and has the potential of aiding the design of new therapies that are guided by neural mechanisms, as well as aiding the allocation of patients to particular treatment modalities. It is also a particularly challenging area of research because most therapies target a range of interacting processes, resulting in complex changes in neural activation, which are also difficult to study over the generally long timeframes of psychological treatment programmes. One success story in this respect has been the elucidation of mechanisms of mental imagery—in general and in its specific relevance for emotional states. The opportunity to study the neural substrates of mental imagery, which came with the development of non-invasive functional imaging methods, particularly functional magnetic resonance imaging (fMRI), has been parallel by an increasing interest in its use in modern cognitive and behavioural therapy approaches. An overview of this field is thus topic for a volume on mechanism

of psychotherapy. In addition, the authors, and a growing international community of clinicians and researchers, have developed an interest in the combination of mental imagery with neuromodulation techniques, particularly neurofeedback. We will argue that the advances in the neuroscience of mental imagery and the increasing evidence for its utility particularly in affective and anxiety disorders now create a unique opportunity to exploit the enhancement of imagery approaches through neuromodulation (and vice versa) for the development of new integrated treatment tools, which may initially focus on depression, post-traumatic stress disorder, and specific phobias, but can, in principle, also be developed for a much wider range of psychological disorders.

MENTAL IMAGERY-BASED TREATMENTS AND IMPLICATED BRAIN NETWORKS

While psychodynamic treatment approaches have analysed the symbolic properties of mental images for decades, cognitive therapies have recently developed efforts to incorporate mental imagery in order to alter affective states and modify their cognitive context (see the study by Edwards (5), and note, for example, the study by Clyne (6) for an active psychodynamic imagery approach). Independently, different mental imagery interventions were developed that aimed to facilitate the effects of mental imagery trough neurofeedback (7–11). By summarising the neuroscientific evidence on mental imagery with and without neurofeedback, this review highlights the potential for cross-disciplinary treatments that combine psychological and neuroscientific tools strategically.

Firstly, the main domains of mental imagery in psychotherapy will be introduced and neuroscientific evidence on their working mechanisms will be discussed. Secondly, psychiatric applications of neurofeedback and the main working mechanisms of neurofeedback trainings will be reviewed. Thirdly, existing evidence on interactions between psychotherapy and neurofeedback approaches will be summarised and future pathways of combining psychotherapy with neurofeedback will be discussed, as well as the potential benefit of brain stimulation techniques.

Mental Imagery in Psychotherapy

Endogenous Generation of Emotional States

A crucial feature of mental images is their ability to induce emotional states (12–14). Taking into account that especially mood and anxiety disorders are marked by dysfunctions of the emotional system, this property of mental imagery has been repeatedly used to induce changes in the affective symptoms of these disorders.

A main category of mental imagery applications used to achieve this consists of repeated mental imagery with positive valence. Repeated positive imagery has been shown to increase the tendency to interpret ambiguous situations as more positive and induce positive mood in healthy participants (15, 16). As depression in particular is marked by pronounced negativity biases (see the review by Gotlib and Joormann (17) for an overview), i.e., the tendency to interpret ambiguous situations as more negative, it can be expected that positive mental imagery will improve depressive symptoms through strengthening positive affective reactions. Accordingly, a recent clinical trial has evaluated positive mental imagery as being effective in reducing such negative biases in depression (18).

Another main category of mental imagery applications consists of mental imagery of specific, fear inducing mental objects or contexts, i.e., imaginal exposure. For example, through imagining fear inducing stimuli that trigger phobic reactions repeatedly, patients can desensitize. This 'imaginal exposure' approach has been successfully implemented in the treatment of a variety of phobias (19–22). Symptoms of other anxiety disorders have also been shown to be significantly attenuated by imaginal exposure, including obsessive-compulsive disorder (23–25) and post-traumatic stress disorder (26, 27).

Controlling Mental Images and Their Cognitive Context

In addition to the two main valence categories of mental imagery (enhancing positive emotions, or imaginal exposure to negative material), some treatment approaches entail switches between negative and positive imagery, for example, imagery rescripting (28–32) or guided imagery (33–35). Switching valence is thereby usually achieved by either changing a mental image to an image with more positive features or wholly replacing it with another image (36). As negative mental imagery constitutes a crucial feature of major psychopathologies (36), it seems not surprising that such substitutions or alterations of negative mental images can be effective across a range of disorders (see the studies by Holmes et al. (37) and Stopa (38) for an overview), including post-traumatic stress disorder (PTSD) (30, 32, 39) and depression (40, 41).

While rescripting aims to alter the content of mental images and, accordingly, also their emotional effect (37, 42), strategies that focus on cognitive control instead aim at changing the interpretations of (mental) images, i.e., their cognitive context (42–44). Here, notably cognitive reappraisal has been widely used to alter the cognitive context of emotion-inducing material (45, 46). Reappraisal has thereby repeatedly been shown to function as an effective emotion regulation strategy, compared to other top-down emotion-regulation strategies as, for example, active suppression (47–49).

Brain Networks Recruited During Mental Imagery

Considering that the main focus of mental imagery applications in psychotherapy lies in influencing emotional processes, an understanding of the neural basis of emotions is fundamental for understanding the neural effects of mental imagery. The current section will therefore provide an overview on the brain systems connecting mental imagery to affective processes (**Figure 1**).

Emotional Experiences Are Associated With Widely Distributed Brain Activation

With the immense growth of available neuroimaging data during the last century, a vast body of empirical evidence has grown that

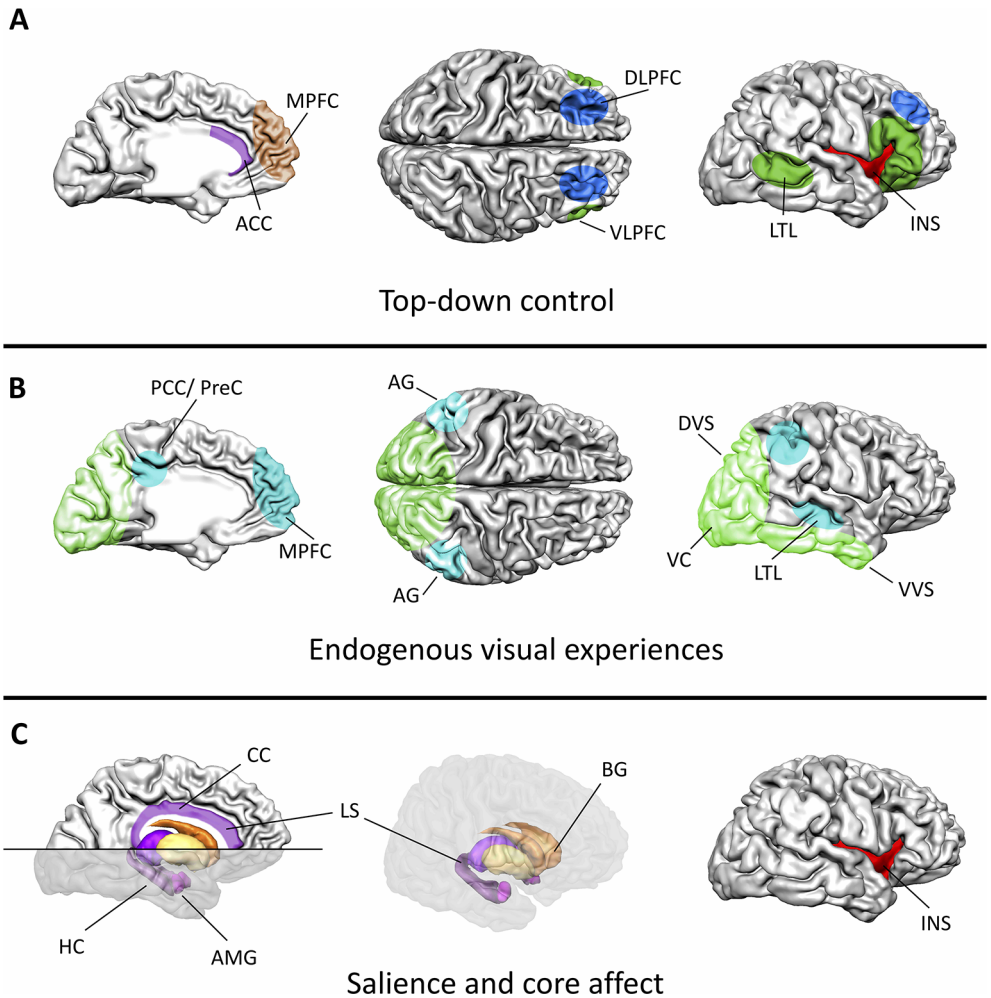

FIGURE 1 | Major functional components and associated brain systems of mental imagery during emotion regulation. **(A)** Cognitive control during mental imagery treatments relies on a distributed cortical network. The dorsolateral PFC and lateral parietal cortex (blue) control mental resources, while the semantic interpretation of the internal state is associated with activation in the ventrolateral PFC and the lateral temporal cortex (dark green). The anterior cingulate cortex (ACC, purple) and the medial PFC (brown) monitor the ongoing processes. The ACC together with the insula (red) thereby function as major connecting hubs between bottom-up saliency information and top-down attentional control. **(B)** Visual experiences during mental imagery mimic actual perception of external stimuli in the visual system (light green). The sensory content of a mental image is thereby activated across different levels of the visual processing hierarchy, ranging from low level visual areas to associate cortices. Modulations in the default-mode-network (turquoise) indicate increased processing of the endogenously generated information. **(C)** Particularly, the limbic system (purple), the basal ganglia (orange/yellow), and the insula (red) encode the hedonic value, arousal, and salience of the visual experience. This information can directly affect ongoing learning processes as particularly the hippocampus is crucially involved in encoding and retrieving emotional memories. The insula, the anterior cingulate cortex, the amygdala, and the ventral basal ganglia form a network that encodes the salience of a generated experience. As a connecting hub between various systems the insula constitutes a key region for introspection during mental imagery. ACC, anterior cingulate cortex; AG, angular gyrus; AMG, amygdala; BG, basal ganglia; DLPFC, dorsolateral PFC; DVS, dorsal visual stream; HC, hippocampus; INS, insula; LS, limbic system; LTL, lateral temporal lobe; MPFC, medial PFC; PCC/PreC, posterior cingulate cortex/precuneus; VC, visual cortex; VLPFC, ventrolateral PFC; VVS, ventral visual stream; CC, cingulate cortex.

helps to relate activation in defined brain structures to emotional experiences. Studies that focused on specific involvement of certain brain regions showed some correspondence between brain structures and emotional states. The amygdala, for example, appears to reliably activate during the experience of fear (50–52). Such findings are in accordance with a body of neuropsychiatric evidence suggesting that lesions in these areas lead to attenuated fear responses (53, 54). Similar findings have been obtained for many other emotional states, e.g., for the insula as being crucial in experience for disgust (55–57) or the orbitofrontal cortex for anger (58, 59).

Although such findings show that activation in certain brain areas can reflect subjective psychological experiences of emotions, they do not imply that activation in these brain structures is necessarily specific to a particular emotional state. Meta-analysis combining data of different emotional states could reliably show that the amygdala contributes to various different emotions (60, 61), with negative as well as positive valence.

Such findings support contemporary constructivist approaches, which constitute that emotional experiences do not emerge from increased activation of single brain structures, but rather from pattern of activation distributed across brain regions that subserve more general functions (see, for example, the studies by Barrett (62) and Lindquist and Barrett (63)). In constructivist approaches, a brain area contributes to an emotional experience by giving rise to one of the many subprocesses from which a holistic emotional experience is constructed. The amygdala, for example, has been implicated in indicating the salience of an emotional stimulus (64, 65) and its involvement in fear has thereby been related to the high salience of fear inducing stimuli. Accordingly, more general functions for various other structures involved in core affect have been suggested (see the study by Lindquist and Barrett (63) for an overview).

Notably, emotional experiences are additionally accompanied by activation in areas that are not directly implicated in core affect (60, 61, 66–68). Across emotional categories, activation increases have been observed in prefrontal areas related to higher order cognitive processes (see the studies by Storbeck and Clore (69) and Duncan and Barrett (70)), the memory system (notably, the medial temporal lobe complex, see the studies by Squire and Zola-Morgan (71); Dolcos et al. (72); Squire et al. (73), and Eichenbaum et al. (74)) or sensory processing (see, for example, the study by Saarimäki et al. (75)), and particularly modulations in visual cortex activity have been observed reliably (61, 76–78). It has therefore been repeatedly argued that emotional experiences arise from distributed neural representations that include affective, cognitive as well as sensory components (61, 69). Particularly, this embeddedness of the affective system into cognitive and sensory networks provides the possibility for mental imagery approaches to alter emotional states by targeting the sensory or cognitive components of emotions.

Brain Activation During Mental Imagery—Similarities With Visual Perception

In accordance with the notion that emotional states are linked to associated sensory experiences, it has been suggested that, during mental imagery, especially, the sensory aspects of a mental image (in contrast to the semantic information contained in it) are fundamental in evoking emotions (36). Indeed, when comparing emotion induction through language to emotion induction by mental imagery, mental imagery evokes stronger emotional responses even when the semantic content is matched between modalities (37, 79). In contrast to actual visual perception, mental imagery is not triggered by external visual stimuli and constitutes a purely mental operation. Interestingly, patterns of brain activation in the visual system during mental imagery resemble activation of weak external visual stimuli (see the study by Pearson et al. (80) for an overview).

A considerable body of experimental psychology and cognitive neuroscience studies suggests that mental imagery can be considered as a form of top-down induced (i.e., internally generated) visual perception, although the exact neural mechanisms are the matter of an ongoing debate. Early fMRI studies revealed reliable brain activation during mental imagery in higher level visual areas, i.e., areas in which visual information is combined to comprehensive visual features (notably the associate visual cortex, early studies by D'Esposito et al. (81); Goebel et al. (82), and Knauff et al. (83). Activation in V1 in turn, i.e., the earliest cortical processing stage of visual information, has also been observed during mental imagery (84–86) but appears to be less pronounced (86) and the ability to form vivid mental images remains preserved after extensive lesioning of V1 (87, 88), supporting that V1 incorporates a less crucial function for the formation of mental images than higher level areas of the visual stream.

Notably, while emotion-related brain activation has been observed in the whole visual cortex, findings for V1 are strongly modulated by the use of visual stimulation in experiments (60). In contrast, higher level visual areas reliably activate also when no visual stimulation is provided (61), suggesting that they serve a more general function in relation to emotions. Crucially, it has been shown that mental imagery is comparably effective as other common mood induction procedures in evoking emotional states (12, 13, 89), underlining that mental imagery can modulate the affective system effectively.

In addition to the cortical pathway which processes complex visual information and gives rise to conscious visual percepts, a subcortical route of visual processing exists for simple, evolutionally meaningful stimuli such as snakes or spiders (90–93). Although the influence of mental imagery on such reflexive sensory-affect connections has not yet been investigated thoroughly, the effectiveness of mental imagery as treatment of the phobias associated with these groups of animals (see, for example, the studies by Lang et al. (94) and Hunt and Fenton (95)) suggests that, at least, the emotional reactivity of subcortical areas involved (prominently the amygdala) can be modulated through mental imagery. However, further research is needed to determine the influence of mental imagery on such basic visual triggers of the affective system. Neurofeedback and other neuromodulation strategies may play a particular role for the synergistic targeting of such limbic circuits.

Memory and Cognitive Control Systems Determine the Context of a Mental Image

While the affective and sensory experiences are intertwined, their relationship is modulated by past experiences and ongoing cognitive processes (96). Taking into account that retrieval of autobiographical memories is commonly associated with mental imagery, an overlapping neural mechanism of episodic memory and mental imagery has been suggested (79, 97). In parallel, it has been shown that mental simulations of fictional events share an extensive neural basis with episodic memory retrieval, including the default-mode and frontoparietal control network (FPCN) (see the studies by Botzung et al. (98); Gerlach et al. (99), and Benoit and Schacter (100)).

In clinical conditions, this interconnectedness of episodic memory and mental imagery appears to be of particular relevance. Several common psychopathologies are characterised by intrusive mental images of emotionally loaded past experiences, and in the case of PTSD, they constitute a core symptom (see

the study by Hackmann and Holmes (101)). Brain activation in relation to such intrusive mental images in PTSD ("flashbacks") has been associated with increased activation in higher-order visual areas in comparison to ordinary episodic memoires (102), supporting the clinical relevance of connections between mental images and the memory system.

While particularly autobiographical experiences have been suggested to contribute to the effects of mental imagery in emotion regulation (79), networks involved in processing the current cognitive context of a percept also strongly contribute to its effect on the affective system (103–105). In this context, anterior prefrontal areas along the midline (particularly the ventromedial PFC and anterior cingulate cortex) have been suggested to integrate incoming information from the limbic system and sensory areas with higher level cognitive goals (96). Lateral prefrontal and parietal areas, in turn, have been suggested to subserve primarily executive functions in the context of emotion regulation. Particularly, activation in the FPCN has been shown to relate to success in emotion generation (106). Interestingly, the FPCN has also been shown to be selectively involved in retrieving visuospatial features of episodic memory (107), supporting the interconnectedness of episodic memory, mental imagery, and emotion.

Different Psychotherapeutic Approaches Target Different Neural Subsystems

Overall, these findings suggest that the neural basis of mental imagery, especially in the context of emotion regulation, spans several different functional domains. Although the recruited networks are highly interconnected and partly overlapping, the different mental imagery-based treatment approaches put more weight on certain subsystems.

Approaches that focus on endogenous generation of emotions through mental imagery (e.g., by using mental imagery to induce positive mood or negative mental images for desensitization) firstly aim at modulating the affective core system. Such endogenous generation of emotions has been shown to involve distributed neural components that interact to create an emotional experience and are shared between positive and negative valance, as well as levels of arousal (106).

For generating the affective core state, particularly the salience network (i.e., a network crucial in determining the saliency of external or internal events) together with the limbic system appears to be crucial. The actual representation of an emotional experience, i.e., an affective state coupled to its mental content, is associated with coactivation of limbic areas, particularly the amygdala and the striatum, and areas related to inward directed attention, particularly the default mode network. Such representations of an emotional state additionally show modulations specific to the mental modality used for emotion generation, i.e., they are accompanied by different activation for mental imagery of visual/autobiographical memories, bodily experience, and semantic strategies. Additionally, before the representation of an affective experience is created, the FPCN has been suggested to initiate the emotion generation processes and, afterwards, contribute to the maintenance of the generated mental representation (106). Due to the role of the FPCN in executive functions and attention, it likely mobilizes and bundles the mental resources necessary to engage in the emotion generation procedure.

While endogenous emotion generation thereby also involves top-down control systems, other treatment approaches target higher order cognitive processes more explicitly. Notably, for cognitive reappraisal, several studies have tried to disentangle the involved brain systems (early studies by Beauregard et al. (108) and Ochsner et al. (109); see also the study by Buhle et al. (110) for an overview). Cognitive reappraisal implies that an emotionally salient event already is present (as the object of the reappraisal, which is represented physically or recalled in memory), this approach does not focus on initiating activation in the core affective system, but rather on altering activation in areas contributing to the cognitive context of the emotional event (which then leads to modulations in the affective core system). In this process, the ventrolateral PFC and the lateral temporal cortex have been suggested to contribute to selecting and representing the semantic context, while the dorsolateral PFC and lateral parietal cortex support shifting the semantic context by modulating the attentional focus towards particular aspects of the mental event and controlling working memory content. In addition, the ACC and the medial PFC have been suggested to monitor ongoing affective and cognitive processing and integrate information from both systems to execute appropriate top-down control (43, 96, 110–112). Most neuroimaging work converges to suggest that cognitive reappraisal is associated with downregulation of the amygdala (110), thereby potentially decreasing the salience of the emotional event.

Neurofeedback Interventions

As mental imagery and emotion regulation recruit defined brain systems, techniques that modulate brain activation can be implemented to support the neural processes that take place in these networks. Additionally, especially neuroimaging-based techniques can thereby provide valuable information on the neural effects of the mental operations that are performed. Neurofeedback approaches combine these two aspects. During a neurofeedback intervention, neuroimaging is applied in order to measure relevant markers of brain activation and feed this information back to participants. By providing neurofeedback during mental imagery, participants thereby become enabled to adapt their mental imagery strategies based on whether the strategies successfully contribute to achieving a desired brain target state.

For several decades, neurofeedback has been created from electrophysiological brain signals acquired through electroencephalography (EEG) (see the study by Kamiya (113) for an overview). While EEG can provide temporally accurate feedback and is accessible to communities, it is a matter for debate whether it can provide reliable signals from deeper brain structures (Nunez et al. (114); Babiloni et al. (115); Burle et al. (116), but see the study by Keynan et al. (117)). Functional magnetic resonance imaging (fMRI) on the other hand, can more accurately narrow down the location in the brain from which neurofeedback is provided and can create neurofeedback from subcortical areas (see the study by Auer and Auer (118)).

Clinical Applications of Neurofeedback

Neurofeedback can be incorporated in psychotherapy because of its active use of psychological techniques, which can range from classical and operant conditioning to explicit imagery and cognitive strategies. This section will review the development of clinical neurofeedback based on fMRI for psychiatric applications. It will focus on fMRI-based neurofeedback rather than incorporate the much larger field of EEG-based neurofeedback because the design of fMRI studies, targeting specific brain regions or networks, has generally followed the considerations of pathophysiological or compensatory networks outlined in the previous sections of this review and has often explicitly incorporated elements of mental imagery.

The clinical development of fMRI-neurofeedback (fMRI-NF) started in 2005 with the publication of a study in patients with fibromyalgia (119). Although conceptually, there should be great promise of such a self-regulation training in patients with chronic pain syndromes relatively little work has followed up on this. In 2011, we published our first study on fMRI-NF in neurorehabilitation, targeting the supplementary motor area (SMA) in Parkinson's disease (120), which was followed up by further studies targeting SMA in neurodegenerative diseases (121, 122). In terms of psychiatric applications, patient studies have mainly been conducted in depression, anxiety disorders, and addiction. In a pilot study of fMRI-NF in depression, we trained patients with depression to upregulate brain networks responsive to positive affective stimuli. This paradigm was modelled on our previous work with healthy participants, which had shown that the neurofeedback component (compared to imagery alone) is required for reliable control over emotion networks (123). The eight patients who underwent this fMRI-NF protocol for four sessions improved significantly on the 17-item Hamilton Rating Scale for Depression, and this clinical improvement was not observed in eight control patients who engaged in a protocol of positive emotional imagery (matched to the fMRI-NF protocol for intervention and assessment times and affective stimuli) outside the scanner (124). In a follow-up randomised controlled trial (RCT) with a similar protocol, we found similar levels of clinical improvement; however, this was also seen for a control intervention using neurofeedback of the parahippocampal place area, an area involved in the processing of scenes and places (125).

A recent RCT pitting upregulation training of the amygdala against upregulation of a control area (the intraparietal sulcus region) found clinical improvement in patients with depression that was significantly stronger in the active (amygdala upregulation) than the control intervention (126). Thus, there is now evidence from RCTs to suggest that fMRI-NF targeting brain networks of emotions may have benefits for patients with depression although it is less clear how specific the protocols/trainings have to be to be effective.

In the area of anxiety disorders, several studies have investigated self-regulation training of the amygdala for PTSD (127–131), and another line of research is targeting the anterior cingulate cortex (131). These have mostly been feasibility studies and information about clinical outcomes is not yet available. Interestingly, both amygdala upregulation (during positive autobiographical memory) (129) and downregulation (during confrontation with traumatic experience) (130) have been employed. Pilot studies have also been conducted in specific phobia (132) and obsessive compulsive disorder (OCD) (133). FMRI-NF has also been piloted for several substance use disorders (134–137) and formal clinical trials are under way(138, 139).

Brain Mechanisms Targeted by Neurofeedback Trainings

Mental imagery is one of the most common strategies reported by participants training to control the neurofeedback signal and often explicitly suggested as a potential strategy by the investigators. For this reason, the same general networks related to self-regulation, emotion, and visual imagery are modulated during these neurofeedback interventions as discussed for the psychotherapeutic applications of mental imagery (124, 140, 141). As a crucial difference to conventional mental imagery approaches, neurofeedback training additionally entails providing information on a subcomponent of these networks to the participant.

Across different psychiatric populations, a common target of fMRI neurofeedback trainings is core emotional areas (**Figure 1**). By providing participants with the opportunity to identify mental strategies that boost/decrease activation in these regions, participants can learn to gain control over their emotional system. This is usually achieved by training participants to increase brain activation in relevant areas during positive mental imagery (123–125, 126, 142) or to decrease activation in areas responsive to negative affective stimuli (143, 144). While neurofeedback provides information on whether a mental strategy is effective in modulating the neural basis of an emotional state, it has also been shown that neurofeedback at the same time stimulates the reward system (141, 145, 146) thereby potentially reinforcing the desired neural target state additionally (see the study by Sitaram et al. (147) for an overview on prominent theoretical accounts on the working mechanisms of neurofeedback).

In addition to inducing changes in the affective core system, neurofeedback approaches can also facilitate specific mental content during mental imagery. In their recent neurofeedback trial in depression, Young et al. (126) showed that positive autobiographical imagery with neurofeedback from the amygdala selectively increases recall of positive memories, even when controlling for general effects of mental imagery. Other neurofeedback approaches have additionally shown that even specific properties of visual representations can be reinforced by neurofeedback. By providing feedback from pattern of activation (rather than only from decreases or increases in averaged regional brain activation), Shibata et al. (148) found evidence that neurofeedback can induce early visual cortex activation related to basic properties of visual stimuli, even in the absence of visual stimulation. While this study by Shibata et al. (148) demonstrated that neurofeedback can modulate low level features of internally generated visual representations, Taschereau-Dumouchel et al. (149) additionally demonstrated that neurofeedback training can also decrease emotional responses to visual-memory

representations of fear inducing animals (see further discussion of this approach in the next section). Overall, the available evidence suggests that neurofeedback can indeed modulate specific mental representations, including perceptual, affective as well as memory components of emotional states.

Prefrontal and parietal control regions implicated in mental imagery are also recruited during most neurofeedback approaches (140, 145), which may reflect the use of mental imagery strategy in neurofeedback training (although other cognitive component processes may also recruit parts of this network). In comparison to mental imagery by itself, however, neurofeedback additionally modulates activation in areas related to reward learning, notably, the striatum (141). While neurofeedback can therefore also be expected to generally reinforce top-down control during mental imagery, it should specifically facilitate interactions between control systems and the neurofeedback target region. Studies investigating changes in brain connectivity have supported this notion by repeatedly showing training-related changes in connectivity between neurofeedback target regions and cortical control regions (150–152). Beyond the general effects of neurofeedback on brain connectivity, contemporary neurofeedback approaches can also target top-down control directly through neurofeedback, for example, by providing feedback from connectivity between control areas and affective core regions (153, 154).

Systematic Combinations of Neurofeedback With Psychological Interventions

By its very nature, a neurofeedback training can be thought of as a psychological as much as a physiological intervention. Many studies use functional localiser procedures, which aim to capture the psychological processes involved in the disorder, such as anhedonia/reduced reward sensitivity in the case of depression, excessive cue reactivity/salience in the case of addictions or excessive fear responses in the case of anxiety disorders. Furthermore, many protocols involve instructions or explicit mood induction strategies, for example, to engage with positive autobiographical memories (155), or offer patients the opportunity to use cognitive strategies learnt in the course of other treatment programmes to try and aid the self-regulation of disease-relevant circuits. In these approaches, mental imagery is commonly an integral part of the intervention. Participants gain control over the neurofeedback signal by identifying the mental content which most strongly affects the neural processes that is regulated. Finally, some studies have used homework exercises to transfer the mental strategies used in the MRI environment into everyday settings, which may be a crucial step to ensure sustainability of any clinical effects.

There is also often a strong element of personalisation. The functional localisers commonly use material that is relevant to the disease process or the putative functional deficit such as positive affective pictures for localisation of emotionally responsive regions in depression (124), contamination scenes in contamination anxiety (133), pictures of spiders in arachnophobia (132), pictures of food to train regulation of food craving (156), or pictures of addictive cues for use in addiction (157). Although generic stimuli from general picture databases such as the International Affective Pictures System will often be sufficient to induce the desired activation patterns (and accompanying physiological responses, e.g., arousal) for many of these protocols, a personalised approach is preferable. For example, if the aim of the neurofeedback training is to target dysfunctional activation patterns that contribute to clinical symptoms directly, the protocol will generally involve induction of these symptoms during the scanning with personalised stimuli. A classical example is OCD, where patients might be asked to take pictures of the scenarios that trigger their symptoms, which can then be used for symptom induction in the MRI environment (158). This approach is parallel to the use of exposure to triggering events in psychological interventions for PTSD. The use of such (personalised) disease-relevant stimuli is not confined to the functional localiser procedure.

In some protocols, such stimuli (images, scripts) are also presented during the neurofeedback runs. One example is the instruction to downregulate amygdala activity during exposure to trauma words (128). In such a scenario, fMRI-NF is incorporated in a broader programme of personalised extinction therapy. Neurofeedback has also been used to pilot a virtual exposure training that would not involve actual presentation of symptom-provoking stimuli but only the reinforcement of the related brain activation patterns. This approach is based on a method called decoded neurofeedback, which entails identification of multivoxel patterns associated with particular stimuli or mental states, which are then used as neurofeedback target (10). In this decoded neurofeedback approach, participants are generally not explicitly told about specific mental strategies, and indeed the basic concept entails that they have no explicit knowledge of the nature of the brain activation patterns being reinforced. In the virtual exposure training, participants then train to increase the occurrence of brain patterns associated with aversive stimuli (which could have been localised in other participants, obviating the need for ever exposing the patient directly to the aversive stimulus) in an operant conditioning task. A pilot study with this paradigm in people showing high subclinical fear for specific animal categories has yielded promising results in terms of attenuation of arousal responses (149, 159).

Neurofeedback treatments, particularly those employing real-time fMRI feedback, thus intrinsically incorporate elements of psychological therapy (exposure, reappraisal and other cognitive strategies, mental imagery) to varying degrees. Indeed, a key element for any clinical implementation of such a technique would seem to be its integration with psychological therapy and training programmes, both in order to harness synergies and ensure sustainability of any effects.

CHALLENGES AND FUTURE DIRECTIONS

Neurofeedback and Mental Imagery

The research discussed in this review highlights the complexity of the neural systems recruited during mental imagery treatments, but also convergent pathways observed across studies that

can be considered as well-validated targets for neurofeedback (**Figure 1**). This review has focused on the visual system because its involvement in mental imagery has been studied in greatest detail, and most clinical applications of mental imagery focus on the visual domain.

However, extensive evidence also suggests that other forms of imagery such as somatosensory or auditory imagery share a defined neural basis with their respective perceptual system (160–163). Additionally, it has been shown that these imagery modalities also modulate affective experiences and their neural basis (106, 164). Notably, individual differences exist with regard to which imagery modality participants prefer, and these differences are associated with differences in effectiveness of mental strategies (164). Future studies will have to evaluate in how far individual patients react better to certain types of mental imagery treatment. Here, neuroimaging and particularly neurofeedback could help to determine whether a certain type of mental imagery is more effective for modulating a neural target in an individual participant compared to other types of mental imagery. This appears to be especially relevant as a major limitation of mental imagery is that mental imagery success is experienced subjectively and mostly reported retrospectively. Such self-report procedures are generally affected by biases, especially when performed retrospectively (165, 166), while verbal reports during mental imagery might additionally distract patients in their mental operations.

Whereas neurofeedback could potentially constitute an objective measure of mental imagery success in the future, variations in applied mental imagery strategies strongly contribute to the heterogeneity of neurofeedback approaches at the moment. In addition to problems that are unspecific to neurofeedback as issues of statistical practice and transparency, particularly, differences in study design and analysis methods have contributed to a pronounced variability between different neurofeedback approaches with fMRI as well as EEG, making it difficult to draw robust clinical or mechanistic conclusions from existing research (see the study by Ros et al. (167) for a contemporary approach to target these issues).

Importantly, a consensus on which criteria should be applied to evaluate success in neurofeedback studies is still lacking. A recent meta-analysis has here made a notable advancement for fMRI neurofeedback by providing an overview on applied success criteria (11) but this information needs to be further utilised to create meta-analytic evidence. Standardising the applied success criteria will thereby enhance the possibility to compare different mental imagery strategies as well as different neurofeedback approaches.

Additionally, heterogeneity in the choice of neural markers used to construct the neurofeedback protocol constitutes a challenge. Most fMRI neurofeedback studies rely on average signals form single regions of interest (e.g., deCharms et al. (119); Haller et al. (168); Zotev et al. (169); Berman et al. (170); Garrison et al. (171); Greer et al. (150)), but several studies have used feedback from activation of whole networks (172, 173), or indices of connectivity between regions (174–177). So far, it is not known if and under which circumstances patients would benefit from training with one marker of neural activity compared to another. Consequently, it is not known whether training a clinically relevant subprocess with a limited number of associated brain regions should be preferred over training distributed pattern of brain activation that better represent the holistic character of an emotional experiences.

Furthermore, the technical set-up of a neurofeedback system additionally creates variance between studies as it determines which markers of brain activation can be extracted: fMRI is characterised by a poor temporal resolution and can therefore not differentiate between neural events that occur close in time. Furthermore, fMRI neurofeedback represents activation that occurred about six seconds before presentation of the feedback. While this delay itself is not necessarily disadvantageous for gaining control over regional brain activation compared to fast changing EEG neurofeedback (178), it constrains fMRI with regard to the information that can be used to create neurofeedback. It remains to be evaluated whether EEG neurofeedback would be preferable for certain psychiatric conditions in which the temporal information contained in the neurofeedback signal has a crucial impact on the treatment outcome.

Further Technical Advances

While this review focussed on combinations between neurofeedback and mental imagery, another major class of neuromodulation techniques that bear potential for modulating brain systems implicated in mental imagery are brain stimulation approaches. These are technical set-ups that stimulate relevant brain areas using electromagnetic currents. Such neurostimulation techniques can generally be divided into invasive approaches, i.e., approaches that require surgery, and non-invasive approaches, that do not. Considering the risks implicated in neurosurgical procedures such as inflammation (179) and the need for restrictive definition of clinical indications, non-invasive neurostimulation techniques are generally more common. However, non-invasive brain stimulation approaches cannot stimulate deep brain structures reliably, with the possible exception of recently developed techniques for focused transcranial magnetic stimulation (180–182).

Due to the problem that deep brain structures can only be reached with invasive brain stimulation techniques, research is considerably sparse with regard to stimulations of subcortical areas during mental imagery but effects of deep brain stimulations on emotional processes have been demonstrated (183, 184). A major role for neurostimulation would therefor entail modulations of cortical areas that can be penetrated with non-invasive brain stimulation techniques. Several studies have shown that interactions between cortical control regions and lower level visual (185, 186) as well as affective areas (187–190) can be evoked through neuromodulation approaches, and stimulation of the dlPFC has been shown to improve the efficacy of emotion regulation (191). While the mechanistic effects of prefrontal and parietal cortex stimulation remain poorly understood (192), stimulation of lateral prefrontal areas has successfully been implemented as add-on treatment for depression (193, 194), furthermore supporting the strong potential of neuromodulation techniques to contribute to treatments of major psychopathologies. Considering that particularly transcranial-magnetic stimulation (TMS) has been

found to be effective for depression, its combination with cognitive behavioural therapy may be promising in this respect (195).

Another direction towards improved interactions between mental imagery and neuromodulation techniques can be expected from approaches that combine neurofeedback with neurostimulation. In such setups a neural target state is achieved by recording brain activation and using information about the current brain state to guide stimulation of brain in order to achieve a certain target state (196–198). In this way, brain stimulation could be used to support the effects of mental imagery during neurofeedback. For example, brain stimulation of limbic areas could help to increase the affective effects of mental images. Moreover, applying brain stimulation and neurofeedback-guided mental imagery successively bears potential. For example, relevant neural systems could first be strengthened with neurostimulation, which does not require active participation of patients. After dysfunctional neural systems have been restabilized, subsequent mental imagery/neurofeedback training could be used to train emotional self-regulation skills and thereby build resilience.

DISCUSSION

Summary

The empirical evidence on mental imagery-based psychotherapeutic interventions supports a role for therapeutic approaches targeting/employing mental imagery in affective and anxiety disorders. As mental imagery can induce emotional experiences by triggering perceptual and memory system components of affective states, while at the same time providing the possibility for goal directed self-regulation, mental imagery can modulate a range of clinically relevant mechanisms. Moreover, a broad range of neuroscientific studies already provides an extensive knowledge based on how the implicated psychological processes are manifested in the brain, opening the door for neuromodulation treatments that facilitate the effects of mental imagery.

From the available neuromodulation approaches, particularly, neurofeedback has already been combined with mental imagery extensively. With the possibility to guide the mental operations to evoke maximal impact on clinically relevant brain systems and the possibility to reinforce associated brain states, neurofeedback provides interesting synergistic opportunities with imagery-based psychological interventions. The beneficial interplay between neuromodulation, cognitive self-regulation, and mental imagery, although this field is still in the early phases of clinical evidence-gathering.

Because mental imagery is one of the most common mental strategies applied during neurofeedback, a much larger amount of empirical research exists for combinations of mental imagery with neurofeedback compared to other neuromodulation techniques. Although neurofeedback protocols often incorporate mental strategies which bear resemblance to psychotherapeutic approaches (such as exposure or positive mental imagery), these parallels have not been exploited so far in a systematic fashion or through combined treatment manuals. Such exploitation remains an attractive task for the collaboration of clinical psychologists, psychiatrists, and neuroscientists.

Conclusion

In conclusion, mental imagery is a core process of many psychological interventions, particularly in affective and anxiety disorders. It has also been a core topic of investigation of cognitive neuroscience, and the neural and psychological mechanisms of mental imagery and its impact on emotional experience have been extensively studied. Based on this knowledge of processes, we can now exploit synergies between imagery and neuroscientific techniques, in order to use the latter to boost the former, or use the former to facilitate the latter. This combination is inherent in many neurofeedback protocols, particularly those employing fMRI signals, but has also been studied with non-invasive brain stimulation. The combination of mental imagery with neuromodulation is conceptually attractive because of the synergistic potential and the potential to achieve more sustainable effects for neurostimulation interventions through transfer to psychological processes.

Yet, the potential treatment combinations are manifold, and the same is true for the neuropsychological subprocesses that could be targeted, so that an extensive body of research is still needed in order to determine the most effective treatment combinations and parameters for this type of neuropsychotherapy.

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Both authors designed, drafted and reviewed this review article.

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Approaching Cognitive Behavior Therapy For Generalized Anxiety Disorder From A Cognitive Process Perspective

Colette R. Hirsch[1,2], Sarah Beale[1], Nick Grey[3] and Sheena Liness[1,2]*

[1] Department of Psychology, Institute of Psychology, Psychiatry and Neuroscience, King's College London, London, United Kingdom, [2] Centre for Anxiety Disorders and Trauma, South London and Maudsley NHS Foundation Trust, London, United Kingdom, [3] Sussex Partnership NHS Foundation Trust, Worthing, United Kingdom

Generalized anxiety disorder (GAD), with uncontrollable worry at its core, is a common psychological disorder with considerable individual and societal costs. Cognitive behavior therapy (CBT) is recommended as the first-line treatment for GAD; however, further investigation into its effectiveness in routine clinical care is indicated and improvement is required in treatment outcomes for worry. Improvements to CBT need to be guided by experimental research that identifies key mechanisms maintaining core aspects of the disorder. This paper summarizes how theory-driven experimental research guided selection and refinements of CBT techniques originally developed by Borkovec and Costello, to target key cognitive processes that maintain worry in GAD. Hirsch and Mathews' model specifies three key research-supported processes that maintain uncontrollable worry in GAD: implicit cognitive biases such as negative interpretation bias and attention bias, generalized verbal thinking style, and impaired ability to re-direct attentional control away from worry. Specific CBT techniques outlined in this paper aim to target these key processes. Clinical data from clients treated using our refined CBT protocol for GAD in a routine clinical care service with a special interest in anxiety disorders were collected as part of service procedures. Large pre-to-posttreatment effect sizes were obtained for anxiety (GAD-7), depression (PHQ-9), and worry (PSWQ) (d=.90–2.54), and a moderate effect size was obtained for quality of life (WASA; d=.74). Recovery was indicated for 74% of cases for anxiety, 78% for depression, and 53% for worry. These findings exceeded most previous effectiveness studies in routine care and were in-line with GAD efficacy trials. This paper also outlines the application of specific clinical techniques selected, adapted or developed to target key cognitive mechanisms which maintain worry in GAD.

Keywords: generalized anxiety disorder, cognitive behavior therapy, attention bias, interpretation bias, verbal worry, attention control

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Liam Mason,
University College London,
United Kingdom

Reviewed by:
Loredana Lucarelli,
University of Cagliari,
Italy
Zoe Maiden,
King's College London,
United Kingdom

****Correspondence:***
Colette R. Hirsch
colette.hirsch@kcl.ac.uk

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INTRODUCTION

Generalized anxiety disorder (GAD) is a common and disabling condition with the hallmark symptom of persistent, excessive, and uncontrollable worry across a number of different topics (1). GAD has an estimated lifetime prevalence in European and American adults of 6–7% (2–5). If untreated, the disorder often persists chronically for decades and demonstrates high relapse rates if remission does

occur (3, 6). Comorbidity with depression-spectrum disorders and other anxiety disorders, notably social anxiety disorder, specific phobia, and panic disorder, is common (4). GAD sufferers report disorder-related impairments in social functioning, occupational functioning, and overall quality of life (7, 8). GAD leads to societal costs associated with increased use of healthcare services and workplace absences (7, 9, 10), with estimated total costs (direct and indirect) of €5308 per patient per year in European samples (11) and estimated healthcare costs of $8613 per patient per year in North American samples (12, 13).

Psychological Therapies For GAD

Given the high prevalence and considerable individual and societal burden of GAD, developing and disseminating efficient and effective interventions is essential. Receiving preferred treatment type impacts clients' engagement and outcomes (14), and people with common mental health conditions, including GAD, exhibit a strong preference for psychological versus pharmacological treatments (15). Current guidelines recommend individual, face-to-face cognitive behavior therapy (CBT) as the first-line treatment for moderate-severe GAD (16–18). CBT refers to a range of interventions that aim to modify maladaptive cognitive processes, which are proposed to maintain psychological disorders such as GAD (19). While CBT was initially developed in the context of depression (20, 21), clinically useful GAD-specific CBT interventions have been developed and tested. A number of CBT protocols are recommended by NICE for use in the UK (e.g. 22–26).

Meta-analyses of randomized controlled trials of CBT for GAD (23, 27–29) consistently support its superiority for reducing anxiety and mood symptoms and improving quality of life post-treatment and long-term, compared to non-intervention and non-CBT control conditions. CBT trials demonstrate large effect sizes for the reduction of the core symptom of worry (30, 31). Unfortunately, the percentage of clients reaching standardized recovery criteria (32), i.e. a score of 47 or below on the Penn State Worry Questionnaire (PSWQ; 33), has been modest, with 46% achieving these criteria post-treatment and 57% at 12-month follow-up in gold-standard trials (31). Hence, despite encouraging results with large effects sizes evident, CBT trials have struggled to get patients below clinical cut-offs and into recovery on the key dimension of worry. To effectively address this core feature of GAD, understanding the cognitive factors that maintain pathological worry and using relevant evidence to inform interventions is important.

Additionally, the generalizability of outcomes from randomized control trials to routine clinical care has been questioned due to greater potential client complexity and lower motivation, as well as less time and resources (34), and therapist deviation from established protocols (35). A meta-analysis of the effectiveness of CBT for the treatment of adult anxiety disorders within routine care included 11 studies on GAD (36). CBT for GAD demonstrated large effects for pre-to-posttreatment reduction of anxiety and depression symptoms that were broadly in line with the comparison efficacy trials selected by the authors of the meta-analysis (22, 37, 38). However, outcomes in the meta-analysis (36) were based solely on generic measures of anxiety and depression, and did not specifically assess pre-to-posttreatment change on the core GAD symptom of worry, which is typically done using the PSWQ. Reliance on generic anxiety and depression questionnaires to assess clinical outcomes in GAD is common practice in routine care.

Given that worry is the defining symptom of GAD, selecting and refining CBT techniques that address the processes underlying pathological worry is essential. Consequently, further investigation of evidence-based CBT that selects interventions to target key processes that maintain worry, as well as anxiety, in GAD is indicated. The following evaluation focuses on disorder-specific and generic outcomes of a CBT intervention designed to target key cognitive-process maintaining pathological worry in GAD provided in a UK National Health Service (NHS) clinical service. First however, research into key processes underlying worry, the scientific basis for the CBT intervention, will be presented.

Key Cognitive Processes Underlying Worry

Given that the central characteristic of GAD is uncontrollable worry, treatment needs to target key mechanisms that maintain worry. In keeping with treatment development for other disorders (e.g. social anxiety disorder; 39; posttraumatic stress disorder; 40), research needs to first identify processes that differentiate GAD and general populations. Subsequently, studies should confirm that the identified mechanism has a causal role in maintaining key aspects of the disorder, i.e. worry in the case of GAD.

Based on Hirsch and Mathews' (41) theoretical model of pathological worry, three key candidate processes trigger and maintain bouts of worry: (i) automatic emotional-processing biases that lead to intrusions of negative thoughts into awareness, and then continue to operate during worry and generate thoughts about more negative potential outcomes, (ii) use of a generalized verbal thinking style during worry that prevents positive resolution and increases the likelihood of further episodes of worry, and (iii) impaired intentional control of attention that impedes terminating an episode of worry and re-focusing onto the task at hand or other non-worry topics.

Automatic Emotional-Processing Bias Favoring Negative Information

GAD is characterized by streams of thinking on wide-ranging topics imbued with emotional ambiguity about negative outcomes. Individuals with GAD exhibit automatic emotional-processing biases favoring negative information.

Interpretation Bias

People with GAD and other common mental health conditions tend to interpret ambiguous scenarios (e.g. "You wake with a start in the middle of the night, thinking you heard a noise, but all is quiet") in a more threatening manner (e.g. "it's a burglar") than non-anxious control participants (e.g. "it was the wind"; 42–44). Participants with GAD are also more likely to produce threat-related spellings of homophones (words that sound the same but have two meanings e.g. dye/die) than non-anxious control participants. Interestingly, people in remission from GAD tend not to differ significantly from control groups (45, 46). Interpretation bias is also reduced following anxiolytic medication (46), with greater clinical improvement associated with correspondingly

reduced negative interpretations. On a recognition memory test for ambiguous sentences, which assessed interpretation bias while avoiding assessor demand effects, participants with GAD endorsed more threatening interpretations than GAD-recovered and non-anxious participants, who performed similarly (47). The groups did not differ in their rejection of threatening but impossible interpretations (foils), thus ruling out the effects of a general threat-based response bias. Using the same task, Krahé et al. (48) further demonstrated that worry was associated with negative interpretation bias across the general population, and that participants with GAD were biased towards negative interpretations, while community volunteers were biased towards benign (i.e. neutral or positive) interpretations. Hirsch and Mathews' (41) model of worry posits a key role for negative interpretations in triggering negative thoughts and maintaining worry. In contrast, a bias to generate more benign interpretations, evident in non-anxious individuals, would lead to less worry being triggered by negative thoughts and to briefer bouts of worry when it occurs, due to benign interpretations having the potential to terminate streams of worry.

Given that there is a negative interpretation bias in individuals with GAD, the next question that must be addressed is whether it has a causal role in maintaining worry and anxiety. One effective approach to investigating causality is to isolate putative causal processes and modify them experimentally. A secondary benefit to this approach is determining how the mechanism can be modified to inform effective psychological intervention methods. Cognitive bias modification (CBM) of interpretation involves repeated practice with tasks that require generation of benign meanings for ambiguous events, or attending to benign interpretations while ignoring threatening meanings.

The causal role of negative interpretation bias in maintaining worry in GAD was initially established using single-session experiments in which participants were trained to generate benign interpretations of ambiguity. Hirsch et al. (49) showed that training high trait worriers to preferentially access benign meanings of emotionally ambiguous homographs (words with two meanings e.g. hit—record or hit—attack), and ambiguously threatening scenarios, led to reductions in worry. Positive training using the same approach was later demonstrated to be effective in reducing worry in participants with GAD on a behavioral task assessing intrusive thoughts, and showed that this effect was mediated by change in interpretive bias (50). These findings provided initial support for the causal role of interpretation bias in the maintenance of worry in GAD. To investigate the longer-term role of interpretation bias, Hirsch et al. (51) allocated volunteers with GAD to receive 10 home-based CBM sessions. CBM involved listening to either ambiguous worry-related scenarios where the ambiguity was resolved in benign ways, or to an active control condition where ambiguity was not resolved. The active training condition led to reduced negative interpretations post-training and, importantly, to reduced levels of trait worry, anxiety and depression at one-month follow-up. Hence, negative interpretation bias has a causal role in maintaining worry and anxiety in people with GAD in the longer term. Consequently, psychological interventions for GAD should focus on developing more benign interpretations of ambiguous situations.

Attention Bias

Another key emotional processing bias proposed in Hirsch and Mathews' (41) model is selective attention to threatening information (attention bias), which heightens perceived threat in the environment, presumably leading to more worry. A typical paradigm to assess attention bias is the dot probe. This involves one threatening and one non-threatening word being presented briefly on screen and subsequently disappearing, with one word then replaced by a probe. Participants categorize the probe as quickly as possible and faster responses are assumed to indicate that the participant was attending to the location of the word that the target replaced. Numerous studies indicate that individuals with GAD preferentially attend to threatening information when simultaneously presented with both threatening and benign stimuli, including words (52–55) and faces (56, 57). However, some research using emotional face stimuli have failed to identify a negative attentional bias in GAD, and instead found faster shifting away of attention from negative faces in this population (58). Given that worry is a verbal process with infrequent imagery (59–61), verbal material may be more appropriate to assess attentional biases in people with GAD. Furthermore, attention bias may operate more clearly when worry has been primed. In high trait worriers, the tendency to attend to threat operated more strongly when tested after an episode of worry (62), creating a self-maintaining cycle in which worry itself may foster greater attention to threat, which in turn could perpetuate worry bouts. Hence, while an attentional bias to threat in GAD has been established, further research on attention biases in GAD is warranted to understand the boundaries (e.g. verbal material akin to worry) and setting conditions (e.g. once worry is activated) of attentional biases in this population.

Attentional bias does, however, appear to have a causal role in maintaining worry and anxiety in GAD. Cognitive bias modification of attention (CBM-A) has been used to test the causal role of attention bias in maintaining worry. Hayes, Hirsch, and Mathews (63) allocated high worriers to benign training or a control condition for a two-stage training session. Participants in the benign training group completed dot-probe training where a target probe replaced the non-threatening word nearly all the time, thus encouraging attention to non-threatening information. In contrast, the probe for the control group replaced threat and non-threat words equally often. Participants then completed dichotic listening training, where one worry story was played into one channel (ear) and one positive story was played into the other channel simultaneously via headphones. Participants were instructed to listen to a specified story, and at random points the story switched to the other ear so participants had to shift attention to the other channel. Participants in the benign group were always instructed to listen to the positive story across all story pairs, thus training them to attend to positive information and away from worry. In the control condition participants were asked to listen to the positive stories for half of the story pairs, and worry stories for the other half. The benign trained group demonstrated a more benign attention bias following training than the control group and also experienced few negative thought intrusions in a subsequent worry task, suggesting that attention bias has a role in maintaining worry. Longer-term attention training using multiple sessions of dot-probe training reduced attentional bias to threat words and importantly also led to

reduced anxiety in people with GAD (64), indicating a causal role of attentional bias in maintaining anxiety in GAD. It should be noted, however, that while important in demonstrating the causal role for attentional bias, multi-session training methods designed to reduce attentional bias have sometimes failed to produce significant change in attention bias in other populations and therefore consequently anxiety (see for example a study in which internet-delivered training at home did not reduce social anxiety; 65). If CBM-A does not change the target process, then its role in maintaining anxiety or worry cannot be assessed. Further refinements to these methods are required to augment home based modification of attention bias. Despite this, evidence of an attentional bias to threat and its causal role in maintaining GAD has been supported, indicating that CBT interventions which facilitate a more benign attentional bias are warranted and may help optimize clinical outcome.

Representation of Threats in Generalized Verbal Form

Thoughts can occur in quasi-verbal form (as if talking to oneself), or imagery form (mental representations encompassing different sensory modalities). Evidence suggests that worry tends to occur predominantly in verbal form, with infrequent and brief images when they do occur (59–61). Furthermore, those with GAD have even briefer and fewer images than those without the disorder (61), in contrast to other anxiety disorders where prolonged negative imagery is common (66, 67).

Individuals with GAD sometimes report believing that worrying verbally is helpful in resolving their problems. This belief is misleading, however, as verbal worry has been found instead to increase subsequent negative thought intrusions (68) and prolong negative mood (69). One likely reason for this unhelpful effect is that verbally represented content in worry is typically over-general in nature, and easily moves from one negative topic to another, making positive resolution of specific problems difficult or impossible. Experiments have shown that intrusive thoughts following negative events are substantially more likely to persist if people are instructed to think about the event verbally (as in worry) rather than in the form of mental images (70). Similarly, Hirsch et al. (68) demonstrated that instructed practice in thinking about worry-related content in the form of mental images, which typically have a more specific and concrete focus, reduced the number of subsequent negative intrusive thoughts compared to engaging in worry in verbal form. Hirsch and Mathews (41) therefore propose that the primarily verbal nature of worry in GAD is particularly unhelpful and leads to greater capture of attention by threatening information (62), utilizes high levels of limited-capacity attention control resources (71) and promotes repeated bouts of worry by increasing the likelihood of subsequent negative thought intrusions (68, 72). Given this, CBT for GAD should encompass techniques that enable more imagery-based and concrete and specific thinking.

Defective Attentional Control

Another cognitive process proposed to underlie worry is impairment in attentional control (41). Attentional control is a limited capacity resource needed to intentionally ignore distracting information or to shift mental focus (73). Inducing active worry impairs attentional control resources (74). Unfortunately, attentional control is depleted in people with GAD (75, 76), with impairment particularly acute during worry (76, 77). Poor performance on attentional control tasks has also been found to predict subsequent development of GAD (78), further suggesting a causal role. Individuals with GAD may struggle to interrupt streams of worry and refocus onto other topics since worry occupies the same limited attentional control resources needed to refocus attention elsewhere. Furthermore, worry in verbal linguistic form may be particularly problematic for individuals who worry excessively. Leigh and Hirsch (71) found that high trait worriers performed poorly compared with low worriers on an attentional control task when worrying verbally, but not when they worried in imagery form. This suggests that the verbal thinking style typical of worry about negative events may be particularly unhelpful and lead to depleted attentional control, the resource needed to shift mental focus away from worry. Biased cognitive processes may combine with defective attentional control to perpetuate worry. Hirsch et al. (49) showed that cognitive bias modification of interpretation, which was designed to train high worriers to interpret ambiguous information more positively, not only facilitated a more benign interpretive bias and fewer negative thought intrusions, but also led to less impairment of attentional control during worry. Hence, interpretation bias may contribute to worry-specific attentional control problems, since more benign interpretations resulted in less pre-emption of attentional control resources by worry content. Given this, uncontrollable worry in GAD may be maintained in part by interpretive bias per se, but also by its on-going impact on attentional control (41). CBT for GAD needs to employ techniques that enable clients to utilize attentional control resources to focus on the task at hand and encourage them to shift away from worry (i.e. choose to deploy the attentional control resources they have on focusing externally). Furthermore, techniques which encourage imagery-based processing or facilitate benign interpretations are likely to also help clients deploy attentional control resources away from worry.

Approaching CBT For GAD From A Cognitive Process Perspective

While traditional CBT (79) focuses on challenging negative thoughts, working at the cognitive content level with GAD can be less efficient, due to constantly shifting worry topics and multiple different perceived negative outcomes for any one worry. Hence, other CBT techniques that afford greater opportunity to change the dysfunctional cognitive processes that maintain worry are preferable. Borkovec's CBT protocol (37, 38) forms the basis for our intervention since it is a gold-standard psychological treatment for GAD, and one of the CBT protocols recommended by the UK National Institute for Health and Care Excellence (18; other protocols include 22, 24, 26). Borkovec and Sharpless (80) outline how they selected and refined their CBT techniques to maximize potential change on key maintaining factors. Tom Borkovec comes from a behavioral perspective, and views behaviours as habits in much the same way as we view cognitive processes as thinking habits in our current approach. Borkovec and Sharpless (80) also highlight the need to focus on processes that appear particularly effective in reducing uncontrollable worry in GAD. Our work builds on this prior tradition of basing

intervention selection for GAD on behavioral research, but draws more on recent relevant findings from cognitive research.

As discussed above, Hirsch and Mathews' (41) integrated model of pathological worry proposes that the three interacting cognitive processes discussed above—habitual cognitive-emotional processing biases towards threat (attention and interpretation), worry in generalized verbal-linguistic form, and depleted attentional control—combine to maintain pathological worry. Consequently, we selected therapeutic techniques and adapted existing interventions to maximize opportunities to target these key cognitive processes, either separately or in combination. Because each causal process can exert its effects on negative thought in different ways (41), achieving optimal improvements is likely to require targeting all of them in CBT. This may be achieved by facilitating more adaptive focus onto benign information (via intentional allocation of attentional control or more automated development of benign attention and interpretation biases), or engagement in more helpful thinking styles (concrete and specific imagery) evident in non-anxious populations. Furthermore, while Borkovec et al., (38) protocol was 16 sessions, routine clinical services—such as those in the UK NHS—aim to offer briefer interventions (e.g. 12 sessions) for anxiety disorders. Consequently, therapeutic techniques need to efficiently leverage change on multiple key cognitive processes.

The Current Study

This paper presents an audit conducted in an NHS routine clinical service of an adaptation of Borkovec et al. (38) CBT protocol to focus on techniques that specifically target key cognitive processes outlined in Hirsch and Mathews (41) cognitive model. Up to 12 weekly sessions were offered rather than 16. The evaluation was conducted on consecutive GAD referrals to a routine clinical service in a UK NHS setting. Change in worry and anxiety were the primary outcomes, as the treatment focused on disorder-specific processes in GAD. Secondary outcomes were change in depression and functioning. Based on previous effectiveness studies of CBT for GAD and on promising evidence for targeting cognitive process variables, we hypothesized that using our revised protocol for CBT for GAD:

1) The intervention would yield significant pre-to-post treatment reduction in levels of pathological worry and anxiety.
2) The intervention would yield significant pre-to-post treatment reduction in levels of depression and functioning.
3) 50% of clients would achieve recovery on the PSWQ posttreatment (which would be in keeping with gold standard RCTs).

METHOD

Ethics Statement

All data were collected as part of routine service procedures/evaluation and thus did not require ethical approval. All patients and therapists were provided with information about how their clinical data was stored and used in routine service provision (81). Data were anonymized and processed in full accordance with the General Data Protection Regulation 2016.

Participants

Participants had a primary GAD diagnosis and comprised 57 consecutive referrals for treatment for GAD at the Centre for Anxiety Disorders and Trauma (CADAT), South London and Maudsley NHS Foundation Trust. CADAT is a routine psychological care service with a specialist interest in the treatment of particular anxiety disorders (e.g. social anxiety disorder; panic disorder) but historically had not focused on GAD. All clients underwent a SCID (82) assessment for GAD at CADAT prior to treatment, and those with comorbidity identified that GAD was the primary problem that they wished to target. Inclusion criteria for the present evaluation included receiving at least one CBT session post-assessment, with clients attending a mean of 11.96 sessions including follow-up appointments (*SD*=2.91). Eighteen clients (31.58%) attended less than the typical and expected 12 treatment sessions, attending between 4 and 11 sessions. Nine of these clients (15.79% of total sample) attended 10 or 11 sessions (and were thus likely to have been given an adequate dose of treatment). Nine attended between 4 and 9 sessions. We performed intention-to-treat analyses including all clients' data, with post-treatment scores on clinical measures derived from the final available session. Demographic characteristics of the client sample are reported in **Table 1**.

Measures

Self-reported symptoms of worry in GAD were assessed with the 16-item Penn-State Worry Questionnaire (PSWQ; 33). Scores

TABLE 1 | Client Demographic Characteristics.

	Client Sample (*n*=57)
Age in years at start of treatment	**Median = 33.00(IQR =13.50, range = 18–65)**
Gender	
Female	75.44% (*n*=43)
Male	24.56% (*n*=14)
Ethnicity	
White	77.19% (*n*=44)
Mixed/Multiple Ethnicity	7.02% (*n*=4)
Black	5.26% (*n*=3)
Asian	1.75% (*n* =1)
Other	1.75% (*n* =1)
Undisclosed	7.02% (*n*=4)
Employment Status	
Full Time	56.14% (*n*=32)
Part Time	19.30% (*n*=11)
Student	10.53% (*n*=6)
Retired	5.26% (*n*=3)
Self-Employed	5.26% (*n*=3)
Unemployed	3.51% (*n*=2)
Long-Term Physical Health Condition(data available for 52 clients)	26.92% (*n*=14)
Taking Psychotropic Medication(data available for 50 clients)	46.00% (*n*=23)
Previous Psychological Treatment(data available for 48 clients)	
Yes—some form of previous treatment	72.92% (*n*=35)
No previous treatment	27.08% (*n*=13)

range from 0 to 8 on each item with caseness threshold total score ≥47 (31) and reliable change index ≥7 (33). The PSWQ has demonstrated good internal consistency α=.91–.95 and test-retest reliability *r*=.74–.93 (33) when measuring disorder-specific symptoms in adults with GAD.

Self-reported anxiety severity was assessed with the seven-item Generalized Anxiety Disorder-7 (GAD-7; 83): range = 0–21, caseness threshold ≥ 8, reliable change index ≥4. The GAD-7 exhibits good internal consistency, α=.92 and test-retest reliability, *r*(ICC)=.83 when measuring anxiety symptom severity in adults with GAD (83).

Self-reported depression severity was assessed with the nine-item Patient Health Questionnaire (PHQ-9; 84): range = 0–27, caseness threshold ≥10, reliable change index ≥6. The PHQ-9 exhibits good internal consistency, α=.89 (84) and test-retest reliability, *r*(ICC)=.84–.96 (85), when assessing the presence and severity of depressive symptoms in adults.

The impact of GAD on clients' work, home and social functioning (functional impairment) was assessed with the five-item Work and Social Adjustment Scale (WSAS; 86). Scores range from 0 to 40, with <10 indicating minimal impairment, 10–20 indicating moderate impairment, and 20+ indicating severe impairment (86). The WSAS exhibits good internal consistency (α=.79–90; 86, 87) and test-retest reliability (*r* =.73; 86) as a measure of disorder-related functional impairment in adults with anxiety disorders.

CBT For GAD Adapted To Target Key Worry-Related Cognitive Processes

Clients with GAD have numerous worry topics at any one time, and shift from topic-to-topic both within and between CBT sessions. Focusing the session can therefore be challenging and therapists may be drawn into "firefighting" individual worries, rather than seeing CBT as a means to develop more benign cognitive processes that can reduce worry in general. Our adaptations to Borkovec CBT interventions (37, 38) introduced or adapted techniques to maximize change on key cognitive process that maintain worry. While other techniques from the protocol are also used, below we discuss ones selected or adapted to target cognitive-emotional processing biases, or deployment of attentional control away from worry. The overarching aim of our adaptations to the protocol focus on helping clients overcome pre-potent cognitive biases and actively focus attention on the task at hand. To foster an understanding of the rationale for the interventions, we have found it useful to use more accessible terms to discuss the cognitive processes targeted in treatment and how more adapted processes can be viewed and developed during treatment. For example, as detailed more below, when talking to clients about worry and how hard it is to shift away worry it can be useful to refer to worry as a "mental magnet" and the need to refocus attentional control away from worry as shifting a "mental spotlight." Cognitive biases are described to clients as "thinking habits" and that new more helpful thinking habits need to be developed via repeated practice. Developing these new thinking habits takes time and repetition, and this is explained to clients in terms of an analogy of repetitions of an exercise at a gym, which will lead to them developing new "mental muscles." The selection and clinical adaptations were guided by the experimental data presented above, and how these techniques aim to target key mechanisms are described below. **Table 2** presents an overview of the targeted processes and the described techniques that target them.

Formulation

Client and therapist work collaboratively to develop an idiosyncratic formulation based on a recent bout of worry. The formulation focuses on processes that trigger and maintain worry such as habits (cognitive-emotional processing biases) of attention and interpretation, as well as highlighting the thinking style being predominantly verbal and abstract in nature. By viewing cognitive biases as mental habits, clients can see that it will take time and effort to change their current tendency to worry, but that new habits can be developed to replace old ones, fostering hope of recovery. Furthermore, the role of depleted attentional control is also discussed in relation to the need to re-deploy a "mental-spotlight" onto the task at hand. The challenge for redeploying the "mental spotlight" is that the "mental magnet" of worry tends to keep the "mental spotlight" focused on worry. "Thinking habits" (i.e. cognitive processes that maintain worry) fuel the "mental magnet" keeping clients focused on their worry. In this way, the formulation highlights key cognitive processes of attention and interpretation biases, verbal abstract worry, and the difficulty of shifting attentional control away from worry and deliberately onto the task at hand.

Other information is also incorporated into the formulation. For example, when drawing out the processes that occur during worry, it can be useful to highlight any self-critical thinking. This often fuels worry and has the potential to undermine efforts to develop new CBT techniques, since if they are not deployed effectively on first attempt self-criticism often follows. This then increases emotional distress and promotes further worry. Consequently, having self-critical thinking style as part of the formulation is useful, and can be later countered by using a compassionate voice (88). The worry process itself also elicits physical symptoms of anxiety, lower mood and poor concentration. In turn, these symptoms can be focused on or interpreted negatively and can fuel more worry. Individuals will often try to respond behaviorally or by actively thinking in certain ways in an attempt to stop worry or deal with the situation. However, these behaviors can often lead back to worry or prove futile. The formulation forms the basis of the intervention, and

TABLE 2 | Worry-Relevant Cognitive Processes and Associated Techniques in CBT for GAD.

Cognitive process	CBT techniques that target the cognitive process
Attention	Formulation, worry history outcome, mental spotlight, worry free zone, worry timetabling, positive data log
Interpretation	Formulation, worry history outcome, positive data log, positive outcome imagery
Verbal thoughts	Formulation, worry history outcome, positive outcome imagery
Abstract generalized thinking	Formulation, worry history outcome, positive outcome imagery
Attention control	Formulation, mental spotlight, worry free zone, worry timetabling, positive data log

provides a rationale for developing more helpful thinking habits (cognitive processes) and trying to shift focus away from worry and effectively onto the current task. Please refer to **Figure 1** for a typical formulation example.

Worry History Outcome Form

Individuals with GAD attend to thoughts around future threat and fail to attend to real benign outcomes for their worries (e.g. worrying about being late for work every day due to traffic, but not registering that they actually always arrive on time). The WHO form is used to record clients worry topics and evaluate whether or not negative outcomes actually occurred. It involves noting the worry topic and date on which the worry occurred, with each topic recorded only once until its outcome is known. In our adaptation of the techniques, clients are also asked to specify the concrete and specific feared outcome of the worry by briefly describing how a film director would set up the scene to show this outcome. This task promotes image-based thinking and ensures that the feared outcome is objective, concrete and specific and testable. Once the event has passed, clients rate whether the outcome was better or worse than expected (i.e. accuracy of the feared prediction) and how well they coped. Hence, the technique targets attention bias by requiring clients to attend to the real, typically positive, outcomes. This process of making an explicit assessment of the specified outcome may in turn provide an opportunity to counter any negative interpretations of the outcome, either at the time the rating is made, or later on reflection with the therapist when reviewing the WHO at subsequent sessions.

Over several sessions the number of worry topics accumulate. Therapists can address clients' negative interpretations regarding their own performance or other's responses generated by reviewing the outcomes; guided discovery highlighting perfectionist standards or viewing the situation less critically (e.g. as if it had happened to someone else) can be useful. After several sessions when situations are rated as better than expected, clients are asked to generate an image of the actual benign or positive outcome for thirty seconds. This is then repeated when any outcome is rated positively and provides practice in generating positive imagery.

After about six sessions of using the WHO form, the percentage of positive/benign outcomes (i.e. better than expected) is calculated for all events that have had an outcome. Borkovec et al. (89) cite that outcomes are better than anticipated 85% of the time. In our experience, rates of positive/benign outcomes very often exceed 95%, perhaps because the task was adapted to include a new column where the main concrete and specific feared outcome is explicitly noted on the form, and thus is more testable. For example, the topic may be "performance review" whereas the specific concrete feared outcome may be "John says I am performing poorly." Personal data around positive outcomes are subsequently built on with a new technique later in treatment (positive outcome imagery—see below). The WHO form is thus used to target attention and interpretation biases, verbal thinking style, generalized and abstract thinking, and attentional control.

Mental Spotlight

Borkovec's protocol (37, 38) involves clients trying to shift focus externally away from worry and onto the task at hand, which is conceptualized in our adaptation as shifting a "mental spotlight." Unfortunately, shifting the mental spotlight onto the task at hand early in treatment is particularly difficult since worry utilizes attentional control, which is the very resource needed to shift attention away from worry. If the client manages to focus on the task at hand, they may find themselves drawn back to the "mental magnet" of worry due to cognitive biases. Additionally, stress and anxiety can further deplete attentional control resources already affected by GAD (76, 90). This makes it more difficult to implement CBT techniques for homework when clients feel most anxious or stressed, and yet this is the very time when they would benefit from CBT techniques the most. CBT homework should consequently be set up as repeated practice in developing new "mental muscles" (via more helpful focus of cognitive processes) to shift the mental spotlight. The aim is to practice the shift—not that people will always be able to be focus away from the worry—so any time the focus comes back on the worry or they are unable to shift, they can see it as another opportunity to practice the shift again. Informing clients that this can be challenging from the start will help them to remain engaged in CBT and see that being compassionate about this challenge, while still attempting to shift to the task at hand, will lead to longer term reductions in worry.

Introducing the concept of attentional control as a mental spotlight that can be difficult to shift and introducing CBT techniques as a way of developing new "mental muscles" that require numerous repetitions to develop helps to address potential barriers to progress with CBT. Over treatment, discussions about what clients will shift their mental spotlight to focus on—conceptualized as "hooks" to draw them in the task at hand—helps clients shift to the task at hand and enables them to remain engaged for longer periods of external focus by identifying particular aspects of a task to focus on. This demonstrates how CBT approaches, conceptualized through metaphors, combine to help clients shift focus away from worry by utilizing their attentional control.

Worry Free Zone

Worry free zones (WFZ) are introduced as the first opportunity to help clients practice focusing their mental spotlight externally onto the task at hand at times when they worry. WFZ were first introduced by Borkovec and Sharpless (80) but have been adapted to highlight the role of cognitive processes that maintain worry. During the first week, WFZ are short (e.g. 5 min) periods of time where clients try to focus away from worry externally onto the task at hand. The zones can be a specified task (e.g. making a cup of tea), place (e.g. bathroom) or time period (e.g. from waking until going downstairs). Clients should be prepared to expect that worry will naturally come back into their mind and to be compassionate with themselves when this happens and re-focus back on the current task. Later, the duration and number of worry-free zones can be increased. WFZ target attention control redeployment actively onto the clients' current task, helping to override prepotent cognitive biases that will focus clients back onto worry. WFZ may also promote attention bias to benign information.

Worry Timetabling

Once clients can shift focus away from worry during WFZ, they could move on to worry timetabling. Worry timetabling requires the client to postpone worries until a specified time later in the day

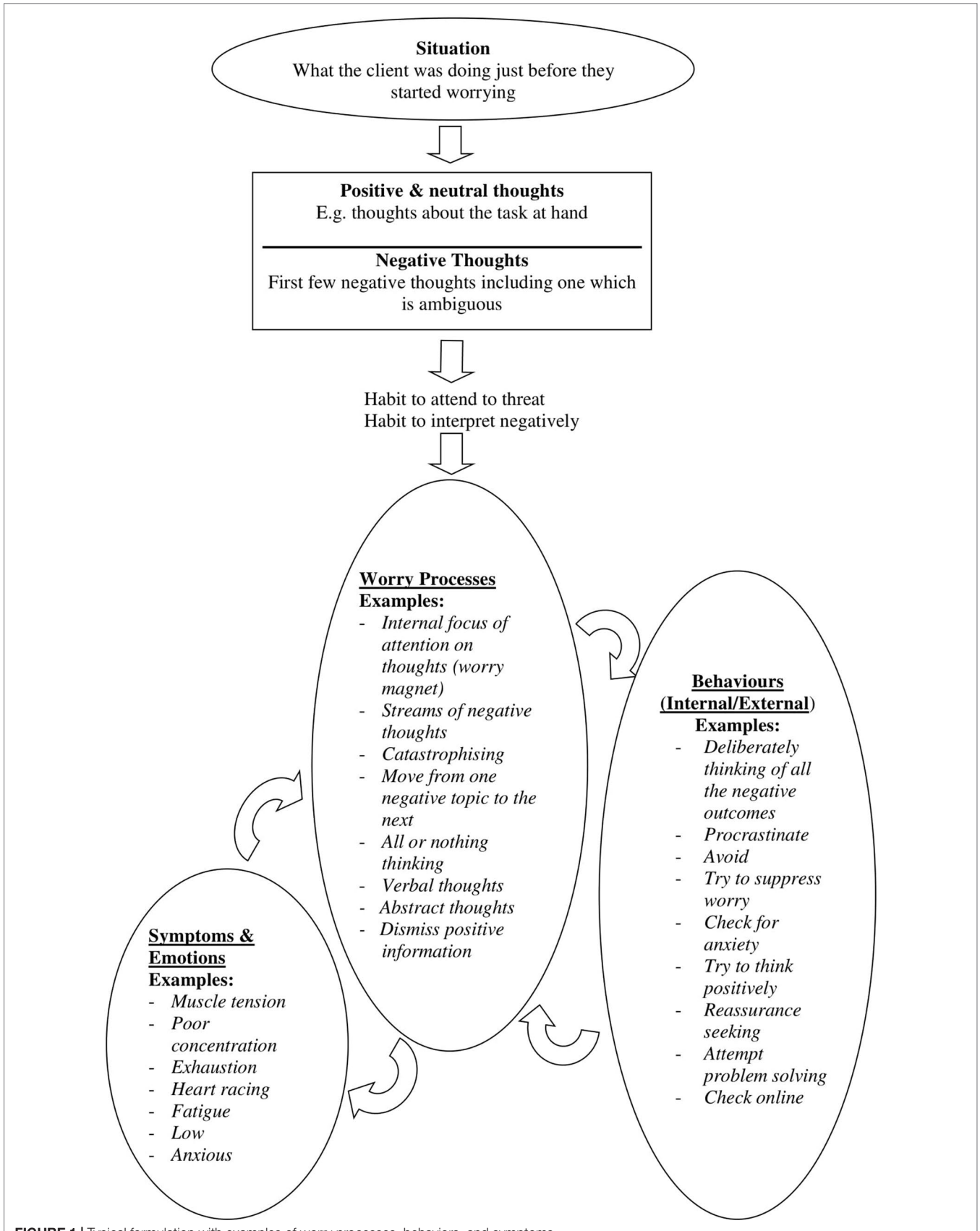

FIGURE 1 | Typical formulation with examples of worry processes, behaviors, and symptoms.

(e.g. 15 min at 5pm) when they catch themselves worrying, and then re-focus their mental spotlight onto the task at hand. Again, clients may need to be reminded of the importance of using their compassionate voice when they notice the worry returning to their mind. Initially worry may return very quickly, but with practice will return less often and with longer worry-free intervals. If clients forget to use the worry period, then they are asked to timetable any subsequent worries to the next day's worry period.

During the first week, the worry period is just left as a time when clients can worry. However, during the following session the therapist will enquire about how the client found the experience of postponing worry, whether the worry returned immediately, and if they persevered with the technique, whether the time between worry bouts about that topic grew longer. The therapist should also enquire about when it was harder and easier to postpone worry to help tailor techniques to facilitate greater ability to shift from worry and remain focused on the task at hand. Clients may subsequently choose to not worry in the worry period, but think about worries in more objective ways, or not at all. The worry timetabling technique utilizes attentional control, which is deployed onto the task at hand, and consequently also helps develop a new attention bias to benign information since most tasks are benign in nature.

Positive Data Log

While not part of Borkovec's protocol (37, 38), keeping a positive data log can help to develop more adaptive thinking habits. Padesky (91) introduced the technique to help develop more adaptive core beliefs by having clients attend to and note down evidence in day to day life that is in keeping with their new alternative (adaptive) core belief. While the current protocol does not focus on core beliefs per se, worry is often driven by a sense that the individual is "not good enough" and so working with the client to collect evidence that they are "OK" in terms of what they do and how others respond to them is useful. The positive data log involves writing down evidence in day-to-day-life that they are OK. Clients can aim to write down a few pieces of evidence on their log each day. It also has the function of getting the client to be a "detective for positive outcomes" and thus helps develop a more benign attentional bias. Furthermore, when identifying potential information for the positive data log, this may also provide an opportunity to generate positive interpretations of ambiguous events in day-to-day life.

Positive Outcome Imagery

Imagery techniques can be used when people are worrying, and the outcome is unknown. Clients identify a current worry topic and specify a concrete and specific feared outcome and rate the percentage likelihood that this outcome will occur. Given that their WHO collation conducted earlier in treatment will indicate that worry topics very often have benign or positive resolutions (85% of the time; 89), clients are requested to brainstorm different ways that this situation could turn out well. This task develops a new habit to generate multiple positive outcomes, rather than multiple negative outcomes characteristic of worry. Clients are then requested to select an outcome or combination of outcomes to think about further in a positive, concrete way. Clients are asked to set-up the scene as if they were a film director, making the outcome concrete and specific. Clients then close their eyes and generate a vivid image of the scenario unfolding, tuning into the different sensory modalities for 2 min. Finally, they re-rate the likelihood the feared outcome would happen. This technique promotes attention to positive information, positive interpretations and concrete and specific positive outcome imagery of future worries.

Procedure

All clients completed at least one CBT for GAD treatment session with a therapist accredited with the British Association for Behavioural and Cognitive Psychotherapies, following an initial assessment. Clients completed clinical measures just prior to assessment (pre-treatment) and at end of treatment just prior to the final clinical session (post-treatment). Two clients did not complete pre-treatment WSAS, so were missing scores at this time point.

RESULTS

Paired-samples t-tests were conducted to compare mean pre-treatment and post-treatment scores for the PSWQ, GAD-7, PHQ-9, and WSAS. Effect sizes of the mean difference for each measure were estimated using Cohen's *d* with Morris and DeShon (92) Equation 8 applied to correct for dependence between means. Significant differences were found between the pre-treatment and post-treatment questionnaire for all measures, with large effects indicated for the PSWQ, GAD-7 and PHQ-9, and moderate effects for the WSAS (small ≥.20, moderate ≥.50, large ≥.80; 93). **Table 3** presents the findings.

Reliable change rates were computed for the PSWQ, GAD-7, and PHQ-9 to assess the clinical significance of change across treatment. Cases demonstrated reliable improvement if their scores decreased between pre-treatment and post-treatment

TABLE 3 | Mean Change in Clinical Outcome Measures Pre- and Post-Treatment.

Measure	Cases with paired scores (*n*)	M_{pre} (SD_{pre})	M_{post} (SD_{post})	*df*	*t*	Cohen's *d*
PSWQ	57	70.72 (6.97)	47.56 (10.84)	56	14.91**	2.54
GAD-7	57	14.16 (5.32)	5.05 (4.06)	56	13.11**	1.74
PHQ-9	57	11.32 (6.59)	5.12 (4.85)	56	6.80**	.90
WSAS	55	15.20 (8.16)	9.49 (7.13)	54	4.47**	.74

***p≤.001.*

PSWQ, Penn State Worry Questionnaire, GAD-7, Generalized Anxiety Disorder -7; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale.

beyond the reliable change index for the given measure (i.e. PSWQ ≥ 7, GAD-7 ≥4, PHQ-9 ≥6; 94). Likewise, cases demonstrated reliable deterioration if their scores increased beyond the reliable change index. No reliable change was indicated if scores changed less than the reliable change index in either direction. The majority of cases demonstrated reliable improvement on the PSWQ and the GAD7, and no reliable change on the PHQ9. Relatively low rates of reliable change on depression (PHQ-9) were probably driven by low pre-treatment depression severity, with only 36 clients exceeding the PHQ-9 caseness threshold for clinically significant symptoms of depression pre-treatment (PHQ-9 ≥10). Of the 36 clients who were above clinical cut off pre-treatment, 72.22% (*n*=26) demonstrated reliable improvement and 27.78% (*n*=10) demonstrated no reliable change. Rates of reliable deterioration for all measures were very low. No reliable change index was available for the WSAS. **Table 4** presents the reliable change findings.

Recovery rates were also computed based on the clinical outcome measures. Cases were considered recovered if they were above the caseness threshold for the measure pre-treatment (i.e. PSWQ ≥ 47, GAD-7 ≥8, PHQ-9 ≥10) and decreased below the threshold post-treatment (94). In keeping with post-treatment recovery rates from gold-standard trials (i.e.46%; 31), over 50% of all cases recovered on the PSWQ. Recovery rates were strong for the GAD-7 and PHQ-9, and substantially exceeded the minimum 50% recovery rate threshold on generic measures stipulated in NHS primary care psychology service guidelines (94). No recovery index was available for the WSAS. **Table 5** presents the findings on recovery.

DISCUSSION

GAD has uncontrollable worry at its core. CBT is a first-line treatment for GAD, so targeting cognitive processes that maintain worry should be a key focus. The current service audit aimed to investigate the effectiveness of CBT for GAD that was adapted to maximize potential impact on key processes which maintain worry, based on an evidence-based cognitive-process model of pathological worry. As predicted, clients demonstrated significant pre-to-posttreatment reduction in worry, general anxiety, and depressive symptoms with large effects (*d*=.90–2.54), and in functional impairment with moderate effects (*d* =.74). Reliable improvement was notably high for anxiety (82%) and worry (95%). Recovery determined by cut off scores was 74% for anxiety and 78% for depression. Also, as predicted, over 50% of cases achieved recovery on worry using the PSWQ (52.6%), in keeping with gold standard clinical trials. These findings demonstrate that formulating with cognitive processes in mind and adapting key techniques to address cognitive processes enables clients to benefit from CBT.

This audit provides evidence of significant treatment effects on both disorder-specific (i.e. pathological worry) and generic (i.e. general anxiety, mood, and functional impairment) clinical outcome measures in line with pre-to-posttreatment effects of efficacy trials of CBT for GAD (23, 29, 31). Notably, effect sizes exceeded previous estimates of effectiveness in routine care for measures of worry, which in our service was *d*=2.54 compared to *d*= 0.61- 0.96 (95, 96), anxiety (our service *d*=1.74 compared to *d*=0.92, 36; and *d* =1.13, 97), and depression (our service *d*= 0.90 in keeping with *d* =.89, 36). These strong outcomes were obtained with 12 sessions, which was briefer treatment than the 16-session Borkovec et al. (38) protocol and many previous effectiveness studies in routine care (12–25 session protocols: 98–100). These findings indicate that tailoring interventions to prioritize potential change on key cognitive processes that maintain GAD can provide helpful and efficient treatment.

The current study also had the benefit of assessing rates of reliable change—or change beyond the measurement error of the given clinical outcome measure—which were promisingly high for pathological worry (95%) and general anxiety (82%). The lower rate of reliable change for depression symptoms (47%) is potentially explained by relatively low pre-treatment depression severity, with a mean pre-treatment PHQ-9 score just exceeding the caseness threshold (total score ≥10), and with 21 clients not meeting depression caseness criteria at baseline. The majority (72.22%) of clients with clinically significant pre-treatment depression scores demonstrated reliable improvement. Recovery rates also exceeded the NHS service targets of 50% for all measures, with the 52% recovery rate observed for the PSWQ in this evaluation in line with meta-analytic posttreatment estimates for gold standard RCTs (46%, 32). Unfortunately, recovery is rarely measured using disorder-specific scales in routine care, as highlighted by Clark (101). The current evaluation also outperformed previous routine care studies in regard to recovery rates for general anxiety symptoms (74% in the current study versus 35%, 98; 43%, 97). Given that effect sizes and recovery rates in the current evaluation were comparable to efficacy trials and exceeded previous routine care studies that focused on GAD in for several relevant clinical outcomes, findings indicate that adapting CBT protocols in line with the emerging evidence-base around underlying processes in GAD may strengthen the outcome of relatively brief treatment in routine care. While results are encouraging, application of the cognitive-process model with CBT may require further refinement to further bolster clinical outcomes, particularly recovery rates on disorder-specific

TABLE 4 | Reliable Change Rates on Outcome Measures.

Measure	*n* cases with paired scores	Reliable Deterioration % (*n*)	No Reliable Change % (*n*)	Reliable Improvement % (*n*)
PSWQ	57	1.75 (1)	3.51 (2)	94.74 (54)
GAD-7	57	1.75 (1)	15.79 (9)	82.46 (47)
PHQ-9	57	1.75 (1)	50.88 (29)	47.37 (27)

PSWQ, Penn State Worry Questionnaire, GAD-7, Generalized Anxiety Disorder -7; PHQ-9, Patient Health Questionnaire.

TABLE 5 | Recovery Rates on Outcomes Measures.

Measure	Cases above Threshold pre-treatment *n*	Recovered % *(n)*	Not Recovered % *(n)*
PSWQ	57	52.63 (30)	47.37 (27)
GAD-7	47	74.47 (35)	25.53 (12)
PHQ-9	36	77.78 (28)	22.22 (8)

PSWQ, Penn State Worry Questionnaire, GAD-7, Generalized Anxiety Disorder -7; PHQ-9, Patient Health Questionnaire.

measures of pathological worry such as the PSWQ. That said, the rates are in keeping with gold standard trials of CBT for GAD, and thus this is also an issue for the field more generally.

While these adaptations were made to the Borkovec protocol (37, 38) and built on Borkovec and Sharpless, (80) focus on selecting techniques which target key behavioral targets, similar adaptations could potentially be used to select and refine key interventions used in other CBT treatment protocols for GAD. Furthermore, the beneficial impact of CBT evidenced in the current audit is attributable to the overall CBT package and we cannot determine what impact our refinements have had. Furthermore, we do not wish to suggest that Borkovec's original techniques, which were designed target behavioral processes, were not critical ingredients for the encouraging clinical outcomes we observed. Indeed, due to this being an audit of routine care, we do not assess mechanisms of change in the current study, which is an important focus for future research.

Recent research has demonstrated that multi-session cognitive bias modification (CBM) for interpretations reduces anxiety and worry in individuals with GAD (51). Examining the feasibility and effectiveness of incorporating these methods into homework for CBT may facilitate greater and more rapid reductions in worry. Furthermore, CBM for interpretation that is enhanced with prolonged imagery and self-generation of outcomes may be particularly helpful in this regard, in a similar manner to using interventions in CBT that target multiple cognitive biases simultaneously. 102) has shown that interpretation training enhanced in this manner augments impact on interpretation bias and could be a promising form of CBM to incorporate into cognitive-process-focused CBT for GAD. Further investigation of clinical outcomes for CBT for GAD incorporating these CBM with imagery and self-generation of outcome is indicated, particularly to determine if this could make face to face CBT briefer.

While the findings from the present evaluation provide encouraging support for CBT for GAD informed by the cognitive-process model of pathological worry, they are subject to several limitations inherent to the naturalistic design. While outcomes were similar to those seen in previous randomized control trials, the present evaluation did not include a control condition. As data were collected as part of routine service procedures, results are not generalizable beyond the specific service context. The clinicians in the present evaluation were also highly trained and experienced in delivering CBT for anxiety disorders, which may preclude representativeness to other routine service settings. Given that the evaluation was based on routine clinical practice, the number of sessions was adapted to clients' needs and constrained by service demands rather than controlled. Only client self-rated outcomes measures were routinely used in the service, and further investigation of clinical change based on independent clinician-rated measures is warranted, given that self-rated measures may exhibit larger effect sizes for pre-to-posttreatment change in anxiety disorders (27). Additionally, while the screening procedures in the present service ensured that DSM V diagnosis was recorded for GAD for all clients, there was insufficient information available to accurately report age of onset, duration of disorder, and comorbidity. The client sample was also majority female (75%), potentially affecting generalizability of the findings. Due to the preliminary nature of this evaluation and data availability, medication status and other potentially relevant clinical and demographic factors were not controlled for in the analyses. As the evaluation was conducted in routine care, it was not feasible to include follow-up of clients. This is a priority of future research, and efficacy trials indicate that effect sizes and recovery rates may be maintained or increase long-term (31, 97, 98). Additionally, it was not feasible to measure therapists' adherence to the protocol and use of each therapeutic technique in the present evaluation. To build upon the encouraging findings of the present evaluation, a full randomized control trial of CBT for GAD informed by the cognitive-process model of pathological worry is warranted in the future. Future trials could enable the important assessment of change in key cognitive processes, assessed using appropriate experimental methods, prior to and following treatment, to determine whether these are ameliorated as desired via CBT and whether these processes mediate longer term reductions in worry and anxiety. Further, if cognitive process-informed CBT for GAD continues to demonstrate promising outcomes in adult samples, adapting CBT for GAD in children and young people based on corresponding evidence of relevant cognitive processes in this population may be warranted.

Conclusion: Techniques that maximize the impact of interventions on key cognitive processes that maintain worry can lead to effective treatment. Formal evaluation of CBT for GAD guided by a cognitive process view of GAD in the form of a full randomized control trial is consequently indicated to continue to strengthen client outcome for this common and debilitating condition.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available as they comprise audit of a clinical service.

ETHICS STATEMENT

All data were collected as part of routine service procedures/evaluation and thus did not require ethical approval. All patients and therapists were provided with information about how their clinical data was stored and used in routine service provision (South London and Maudsley NHS Foundation Trust, 2011). Data were anonymised and processed in full accordance with the General Data Protection Regulation 2016.

AUTHOR CONTRIBUTIONS

CH, SL, and NG contributed conception and design of the study. SB created the database and performed the statistical analysis. CH and SB wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Emotional Mental Imagery Abnormalities in Monozygotic Twins With, at High-Risk of, and Without Affective Disorders: Present in Affected Twins in Remission but Absent in High-Risk Twins

Martina Di Simplicio[1], Alex Lau-Zhu[1,2,3], Iselin Meluken[4], Patrick Taylor[1], Lars Vedel Kessing[4], Maj Vinberg[4], Emily Alexandra Holmes[5,6] and Kamilla Woznica Miskowiak[4,7]*

[1] Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, United Kingdom, [2] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom, [3] Medical Sciences Division, Oxford Institute of Clinical Psychology Training, University of Oxford, Oxford, United Kingdom, [4] Copenhagen Affective Disorder Research Centre (CADIC), Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [5] Division of Psychology, Department for Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, [6] Department of Psychology, Uppsala University, Uppsala, Sweden, [7] Department of Psychology, University of Copenhagen, Copenhagen, Denmark

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Liam Mason, University College London, United Kingdom

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Sarah Kittel-Schneider, Universitätsklinikum Würzburg, Germany
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***Correspondence:**
Martina Di Simplicio
m.di-simplicio@imperial.ac.uk

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Background: Mental imagery abnormalities feature across affective disorders including bipolar disorder (BD) and unipolar depression (UD). Maladaptive emotional imagery has been proposed as a maintenance factor for affective symptomatology and a target for mechanism-driven psychological treatment developments. Where imagery abnormalities feature beyond acute affective episodes, further opportunities for innovation arise beyond treatments, such as for tertiary/relapse prevention (e.g., in remitted individuals) or primary prevention (e.g., in non-affected but at-risk individuals). The aim of our study was to investigate for the first time the presence of possible mental imagery abnormalities in affected individuals in remission and at-risk individuals for affective disorders using a familial risk design.

Methods: A population-based cohort of monozygotic twins was recruited through linkage between the Danish national registries (*N*=204). Participants were grouped as: affected (remitted BD/UD; n = 115); high-risk (co-twin with history of BD/UD; n = 49), or low-risk (no co-twin history of BD/UD; n = 40). Twins completed mental imagery measures spanning key subjective domains (spontaneous imagery use and emotional imagery) and cognitive domains (imagery inspection and imagery manipulation).

Results: Affected twins in remission reported enhanced emotional mental imagery compared to both low- and high-risk twins. This was characterized by greater impact of i) intrusive prospective imagery (Impact of Future Events Scale) and ii) deliberately-generated prospective imagery of negative scenarios (Prospective Imagery Task). There were no significant differences in these key measures between affected BD and UD

twins in remission. Additionally, low- and high-risk twins did not significantly differ on these emotional imagery measures. There were also no significant differences between the three groups on non-emotional measures including spontaneous imagery use and cognitive stages of imagery.

Conclusions: Abnormalities in emotional prospective imagery are present in monozygotic twins with affective disorders in remission—despite preserved cognitive stages of imagery—but absent in unaffected high-risk twins, and thus do not appear to index familial risk (i.e., unlikely to qualify as "endophenotypes"). Elevated emotional prospective imagery represents a promising treatment/prevention target in affective disorders.

Keywords: mental imagery, future simulation, bipolar disorder, depression, twins, endophenotype

INTRODUCTION

Mental imagery refers to the experience of perception in the absence of external sensory input, for example "seeing in the mind's eye" (1). Cognitive science suggests that mental imagery is more emotionally-evocative than its verbal-based counterpart (2). Emotional imagery symptoms feature across affective disorders (3–6). Clinical formulation in psychology suggests such mental imagery contributes to the disorder maintenance, and as such imagery presents opportunities for treatment innovation, especially for areas of considerable clinical challenge such as bipolar disorder/BD (7) and anhedonia in unipolar depression/UD (8). In psychopathology, adaptive positive imagery can also be promoted (9–11), and conversely, maladaptive negative imagery can be disrupted (12–15).

Imagery—in models of psychological treatments—has been primarily conceptualized as a maintenance ("proximal") factor, i.e., keeping the disorder going once it developed. Delineating the role of imagery throughout illness progression and outside of the illness episode can help map other areas of application that stand to gain from a focus on imagery. For example, emotional imagery abnormalities, which are (causal) risk factors proceeding disorder onset, might be addressed to prevent disorder emergence (i.e., primary prevention). Likewise, imagery abnormalities that persist in remission can serve as target for keeping the individual well and preventing relapse (i.e., tertiary prevention). Importantly, identifying potential cognitive maintenance and/or risk factors paves the way for testing mechanistic hypotheses and mechanism-based interventions—both psychological and pharmacological (16).

Affective disorders (UD and BD, defined as disorders in which the fundamental disturbance is a change in affect or mood to depression) (17) hold one of the highest burdens of disease worldwide (18). There is a need for better identification of risk and resilience markers to develop better therapeutic interventions at different stages of disease. Affective disorders present variable degrees of heritability, from high rates in BD (19, 20) to moderate rates in UD (20).

Biases in cognition—in both "cold" (non-emotional) and "hot" (emotional-laden) information processing spanning domains of perception, attention, memory, and learning—have been associated with acute disorder episodes (21, 22) well as after recovery from acute episodes (23, 24) and in familial risk (25). Cognitive abnormalities that persist in remitted states (i.e. are state-independent) may represent illness-related traits, conferring cognitive vulnerability for relapse (26, 27). If trait-abnormalities also meet further criteria such as heritability and higher frequency in individuals at familial risk compared to the general population, these may constitute "endophenotypes" of the disorder—i.e., potentially lying along the causal pathway between genes and disorder (28)—which could guide the discovery of genetic etiological mechanisms and inform clinical efforts including preventative strategies targeting such mechanisms in disorders with high genetic risk.

Emotional imagery has been proposed to be an "emotional amplifier" that drives both depressive/anxiety and manic symptoms in BD (29). Such images may depict aspects of the future, thought to underline associated emotions and behaviors such as wellbeing, prediction, and planning (30, 31). BD and UD have both been associated with heightened involuntary and intrusive prospective imagery (32–34)—more recurrent and impactful images of personally-relevant future real-world scenarios that spring to mind unbidden (e.g., an upcoming job interview). BD and UD have also been associated with more vivid and "real" future negative images that are deliberately-generated, such as under direct instructions in the laboratory to imagine in response to statements such as "someone close will reject you" (32). Some phenomenological aspects may show more disorder-specific profiles. For instance, imagery can be "overactive" in positive states in BD only (32, 35) possibly driving escalation to mania similar to other positive emotion biases (36), and suicidal imagery may be more "compelling" in BD compared to UD (37) in line with higher suicidal rates in BD (38, 39).

There is a paucity of studies of cognitive (non-emotional) aspects of mental imagery in affective disorders, such as studies based on a key computational model that identifies four cognitive stages of mental imagery (1, 40). In this model, mental images are thought to be initially created from either short-term or long-term memory (i.e., generation); once held in mind temporarily avoiding immediate decay (i.e., maintenance), such images' characteristics can be interpreted/scanned (i.e., inspection) and further transformed (i.e., manipulation). Available evidence

from one study in UD points to potential deficits in both imagery generation and manipulation (41). The only study simultaneously assessing emotional and cognitive domains of imagery across affective disorders showed that in BD performance on non-emotional imagery tasks may vary depending on the cognitive stage tested, with deficits present in imagery manipulation alongside superior performance in imagery maintenance (32).

To date, imagery research on BD and UD has primarily involved individuals with mix of acute and recovered depression episodes (32, 33, 35, 37), and abnormalities remain untested for remitted states in affective disorders.

Imagery may also play a role in the etiology of affective disorders, i.e., involved also in the initial emergence of the disorder. This is supported by abnormalities detected in non-clinical samples with subclinical features of BD and UD (42–45) and UD (30, 46, 47). Nevertheless, it is unclear whether or not such imagery-based abnormalities reflect *familial* risk and represent candidate "endophenotypes" for affective disorders (28).

The present study investigated the presence of imagery-based abnormalities in a population-based cohort of monozygotic twins, grouped as affected (remitted or partially-remitted twins with personal history of BD/UD), high-risk (unaffected twins with co-twin history of BD/UD), and low-risk (unaffected twins with no co-twin history of BD/UD). Participants completed assessments of subjective domains of mental imagery and cognitive (non-emotional) imagery stages, informed by our previous research (32, 40).

Our primary aims were to delineate whether imagery abnormalities i) persist in remission (by comparing affected twins in remission versus unaffected low-risk twins); and ii) are present in twins at high familial risk for affective disorders (by comparing high-risk twins versus both remitted and low-risk twins). If both i) and ii) were true, this would be consistent with the proposition that imagery abnormalities are candidate "endophenotypes" of affective disorders. Further, we conducted exploratory analyses separating BD from UD; comparing BD *vs*. UD affected twins directly; and assessing imagery-symptom links transdiagnostically.

METHOD

Participants

A nationwide record linkage of the Danish Twin Registry (48) and the Danish Psychiatric Central Research Register (DPCRR) (49) identified eligible monozygotic twins. In addition to monozygosity, eligibility criteria were i) a personal or co-twin history of an affective spectrum diagnosis (i.e. International Classification for Diseases ICD-10 codes F30-34.0 and F38.0) (17) or for low-risk twins neither a personal nor a co-twin history affective spectrum diagnosis from January 1995 to June 2014, and ii) age 18–50 years.

Exclusion criteria for all groups were: birth weight under 1.3 kg, history of brain injury; current severe somatic illness, current substance abuse; current mood episode defined by Hamilton Depression Rating Scale (HDRS-17) (50) or Young Mania Rating Scale (51) (YMRS; scores >14), current pregnancy, or being dizygotic. The low-risk twins were also excluded if they reported other first-degree relatives with organic mental disorder, schizophrenia spectrum, or affective disorders.

Participants provided their written and informed consent to the study in accordance with the Helsinki declaration. The study was approved by the ethics committee for the Capital Region of Denmark (H-3-2014-003) and the Danish data protection agency (2014–331–0751).

Recruitment took place from December 2014 until January 2017. From an initial sample of 215 participants, 11 participants were excluded due to missing diagnoses ($n = 6$), affective disorder ($n = 4$), or alternative high-risk affective disorder ($n = 1$). The final sample for this paper included 204 participants, with each classified as affected ($n = 115$; BD = 31 and UD = 84), high-risk ($n = 49$; BD = 11 and UD = 38), or low-risk ($n = 40$). There were 25 concordant affected twin-pairs (BD/BD: $n = 5$; UD/UD: $n = 11$; BD/UD: $n = 9$), 45 discordant twin-pairs (high-risk/UD: $n = 36$; high-risk/BD: $n = 9$), 19 low-risk twin pairs, and 26 single twins.

Overall Procedure

Participants attended a 1-day assessment at the Danish Research Centre for Magnetic Resonance at Copenhagen University Hospital Hvidovre. Further data from this sample have been reported elsewhere, including neurocognitive (52–55), clinical/psychological (56), and biological outcomes (57). Here we report data on assessments related to mental imagery for the first time.

Assessments

Clinical Characteristics

Diagnoses of psychiatric illness were assessed with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (58). Ratings and a SCAN interview were conducted by two PhD students blinded to the DPCRR register diagnoses. The research diagnoses obtained from the SCAN interviews determined the final assignment to groups. Pre-morbid intelligence (IQ) was assessed with the Danish Adult Reading Task (59). Depressive symptoms were assessed with the HDRS-17 (50). State anxiety was assessed with the State-Trait Anxiety Inventory form-Y (STAI-Y) (60). Manic symptoms were assessed with the YMRS (51).

Subjective Domains of Mental Imagery

Spontaneous Imagery Use

The Spontaneous Use of Imagery Scale (SUIS) (61) is a 12-item self-report scale which measures the use of non-emotional mental imagery in daily life. Each item is rated on a 5-point Likert-type scale. Total scores range from 12 to 60, with higher scores indicating greater use of imagery. An example item is "When I think about a series of errands I must do, I visualize the stores I will visit".

Emotional Mental Imagery

Three assessments were considered to gauge various aspects of emotional imagery. The *Impact of Future Events Scale (IFES)* (62)

is a 24-item self-report scale which is used to assess intrusive (involuntary) future-oriented imagery. Participants were asked to identify three future events which they had thought about or imagined over the previous week, and state whether each was positive or negative. Participants then responded to 24 statements about prospective imagery in relation to these events. Each item is rated on a 5-point Likert-type scale. Total scores range from 0 to 96, with higher scores indicating greater emotional impact of *involuntarily-generated* prospective imagery.

The *Prospective Imagery Task (PIT)* (63) is used to assess aspects of deliberately-generated (voluntary) imagery for imagined future events. Participants were presented with 10 positive and 10 negative hypothetical future scenarios and asked to generate a mental image of each. They were then asked to rate each image of a 5-point Likert-type scale, assessing vividness, likelihood of the event occurring to them, and how much they felt as though they were experiencing the event while imagining it. Total scores for each dimension range from 20 to 100, with higher total scores indicating greater subjective experience of *deliberately-generated* prospective imagery.

The *Mental Imagery Interview (MII)* (32) is a semi-structured interview which contains 12-items each for low-mood, anxious, and high-mood states. It explored the subjective experience, occurrence, and content of a significant mental image in each mood state, retrospectively. Each item is rated on a 7-point scale (from -3 "not at all" to 3 "extremely"), or 9-point scale (from 1 "not at all" to 9 "extremely"). Higher scores indicate greater emotional impact of the image.

Cognitive (Non-Emotional) Stages of Mental Imagery

Imagery Inspection

This is considered the third stage of cognitive mental imagery (1) and can be assessed with the Letter Corner Classification Task (LCCT) (64). This task involves assessing the object-based spatial characteristics of four block capital letters (F, N, Z, G). Each letter was marked with an asterisk in the bottom left corner, and an arrow travelling clockwise around the letter. The task was split into three stages, each involving the letters being presented, which participants were asked to memorize, followed by the letters being removed from sight. In stage one, participants were then asked to reproduce each letter, starting at the asterisk and moving clockwise. In stage two, participants were asked to categorize the corners of each letter as "top" or "bottom" by moving clockwise around the letter, starting from the asterisk and indicating "yes" if the corner is at the extreme top or bottom of the letter, and indicating "no" otherwise. In stage three, participants were asked to categorize the corners of each letter as "outside" or "inside", by moving clockwise around the letter, starting from the asterisk and indicating "yes" if the corner is at the extreme left or right of the letter, and indicating "no" otherwise. Error rates and response times were recorded.

Imagery Manipulation

This is considered the fourth/final stage of cognitive mental imagery (1) and can be assessed with the Mental Rotation Task (MRT) (65). In a computerized version of the MRT, participants were shown pairs of three-dimensional line drawings and asked to decide whether the drawings were of the same rotated object or of different objects. Participants completed a practice trial followed by three progressively more difficult levels of transformation, based on the angular disparity between the two shapes (easy: 50; medium: 100; difficult: 150). Error rates and response times per difficulty level were recorded. Two performance parameters were derived based on response times (41, 66): i) the intercept-index, deemed to represent the sensory-motor component of task response, and ii) the slope-index, deemed to represent the spatial-ability (imagery-based) component of task response.

Statistical Analyses

Outliers above or below three standard deviations (*SDs*) of the mean were excluded. Groups were compared on baseline and clinical characteristics and on key outcomes from each imagery assessment based on previous literature (32). Each continuous dependent variable was examined with mixed-model analysis of variance with groups as fixed factors and modeling random effects for twin pairs to account for dependence within these. Categorical variable (sex only) was examined with logistic regression with groups as predictors and within twin-pair dependence adjusted for using generalized estimating equations estimates of the standard errors.

For our primary analyses, we included our three key groups, i.e., affected in remission (combining BD and UD), high-risk and low-risk, followed by pairwise comparisons when relevant. Comparing the affected (remitted) group with the low-risk group would help determine whether and which imagery abnormalities persist in remission; comparing the high-risk group with the other two groups would help determine whether and which imagery abnormalities are present in individuals who have not developed BD/UD despite genetic liability (consistent with the notion of an endophenotype for affective disorders). Effect sizes as Cohen *d* (67) were included to aid interpretations (0.30 = small; 0.50 = medium; 0.80 = large).

We conducted three additional sets of secondary (exploratory) analyses. First, we repeated the above analyses with only BD or UD on selected imagery measures for which previous literature indicates discrepancy between disorders (and hence combining both groups may not be always appropriate): i) emotional imagery of positive valence (PIT and MII) may be enhanced in BD only (35, 68, 69) and ii) aspects of mental rotation performance may be affected in BD (32) and UD (41). Second, we directly contrasted the BD and UD affected (remitted) groups, as previous studies have contrasted imagery measures between BD and UD groups predominantly during depression illness at the time of assessment (32). Finally, we conducted a series of multiple linear regressions with baseline clinical characteristics (HDRS and STAI-Y) as predictors, and key imagery outcomes (emerging as significant from our primary analyses) as dependent variables, based on our previous research demonstrating associations between emotional imagery and symptoms transdiagnostically (32). Manic symptoms (YMRS) were not included as these were matched between groups (see Results). Initially both predictors were entered simultaneously, and then non-significant predictors were removed from the model stepwise until only significant predictors remained.

Significance level was set to alpha = .05 for two-sided hypothesis-testing (unless otherwise stated for directional hypothesis-testing). As our primary analyses involved multiple comparisons, we also applied the Benjamini-Hochberg procedure (70) to control for family-wise false discovery rate (q = .10), and we reported these when they changed the pattern of results (for one pairwise comparison only). Data analyses were conducted using SPSS (71).

RESULTS

Baseline and Clinical Characteristics

Means and SDs are presented in **Table 1**. There were no significant group differences in sex, age, education, or IQ. As expected, the affected twins scored higher (than high-risk and low-risk groups) on baseline symptoms of depression and anxiety, but there were no significant differences between high-risk and low-risk twins. There were no significant group differences in symptoms of mania. A high proportion of affected twins in remission reported current pharmacological medications (**Table 1**). Restricting our primary analyses to twins without medication did not change the pattern of results, hence we report results including all twins.

Subjective Domains of Mental Imagery

Spontaneous Imagery Use

Overall group difference in SUIS scores was not statistically significant (**Table 2**), indicating an absence of between-group differences in spontaneous use of non-emotional imagery in everyday life.

Emotional Mental Imagery

For the *IFES* (assessing the impact of intrusive future imagery), the overall group difference in total scores was statistically significant (**Table 2**). Affected twins in remission had higher IFES scores (indicating higher impact of intrusive prospective imagery) both relative to low-risk twins ($F_{(1, 89.93)} = 8.60$, $p = .004$), and to high-risk twins ($F_{(1, 85.70)} = 15.49$, $p < .001$). Low- and high-risk twins did not differ significantly in IFES scores ($F_{(1, 52.28)} = 2.77$, $p = .102$).

For the *PIT* (assessing the impact of deliberately-generated future imagery), overall statistically significant group differences were consistently found in response to imagined *negative* future scenarios (**Table 2**). Affected twins in remission rated negative future scenarios as more *vivid* than low-risk twins ($F_{(1, 72,58)} = 7.64$, $p = .007$), and also than high-risk twins ($F_{(1, 98.21)} = 6.54$, $p = .012$). Affected twins in remission rated these scenarios also as more *likely* to occur to them than low-risk twins ($F_{(1, 70.70)} = 4.70$, $p = .034$), and also than high-risk twins ($F_{(1, 91.31)} = 10.05$, $p = .002$). Finally, affected twins in remission reported "*experiencing*" these scenarios while imagining them, more so than low-risk twins ($F_{(1, 55.08)} = 19.16$, $p < .001$), and also than high-risk twins, ($F_{(1, 126)} = 6.91$, $p = .010$). The low- and the high-risk twins did not statistically significantly differ in ratings of vividness, likelihood (F's <1), or "experiencing" ($F_{(1, 41.10)} = 1.93$, $p = .173$).

In contrast, overall statistically significant group differences in response to deliberately-generated imagery of *positive* future scenarios were found for ratings of *likelihood* only, but not for ratings of vividness or "experiencing" (**Table 2**). Pairwise comparisons showed affected twins in remission rated positive future scenarios as *less likely* to occur to them than low-risk twins ($F_{(1, 63.1)} = 3.74$, $p = .058$), and also than high-risk twins ($F_{(1, 94.66)} = 6.90$, $p = .010$), but there were no statistically significant differences in the latter two groups ($F < 1$). When controlling for false discovery rate, the latter pairwise comparison between affected twins and low-risk twins was no longer significant.

In the *MII* for low-mood states, there were no statistically significant overall group differences in time spent thinking in images (frequency), nor in ratings of images as "real" and "compelling" (**Table 2**). However, there were statistically significant group differences in how "demotivating" the image

TABLE 1 | Baseline and clinical characteristics of affected, high-risk, and low-risk monozygotic twins for affective disorders.

	Affected (BD+UD; remitted)			High-risk			Low-risk			Overall group difference		
	M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*F*	*df*	*p*
Age (years)	36.10	8.83	115	36.94	9.58	49	37.07	9.18	40	< 1	2, 98.94	.868
Education (years)	14.53	3.26	115	15.69	3.14	49	15.50	2.61	40	2.14	2, 107.06	.123
IQ	113.53	6.36	109	112.44	6.74	48	114.04	5.69	40	1.36	2, 110.87	.261
HDRS-17	4.84[a]	3.55	115	2.73[b]	2.46	49	1.89[b]	2.11	40	16.24	2, 114.35	< .001
STAI-state	31.81[a]	7.54	115	28.78[b]	6.78	49	26.98[b]	6.90	40	7.59	2, 170.98	.001
YMRS	1.83	2.13	115	1.51	1.31	49	1.25	1.53	40	1.54	2, 184.61	.217
	n	%		*n*	%		*n*	%				
Sex (female)	82	71		33	67		32	80		Wald chi-square (2, N = 204) = 1.30, p = .522		
Medication (yes)	63	55		3	6		0					
Antidepressant	45	39		1	2		0					
Mood stabilizer	22	19		0			0					
Antipsychotic	18	16		0			0					

BD, bipolar disorder; UD, unipolar disorder; HDRS-17, Hamilton Depression Rating Scale; IQ STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale.

TABLE 2 | Subjective domains of mental imagery in affected, high-risk, and low-risk monozygotic twins for affective disorders.

	Affected (BD+UD; remitted)			High-risk			Low-risk			Overall group difference			Effect size (d) of pairwise comparisons		
	M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*F*	*df*	*p*	*AF vs. LR*	*AF vs. HR*	*HR vs. LR*
SUIS	37.25	9.70	104	36.81	9.55	42	36.30	7.20	37	<1	2, 139.39	.942	0.18	0.08	0.08
IFES	33.48	15.37	88	25.21	13.88	38	19.00	10.61	32	11.46	2, 137.19	<.001	1.11	.68	.52
PIT															
Negative															
Vividness	2.70[a]	0.84	91	2.26[b]	0.85	38	2.17[b]	0.90	36	5.74	2, 156.05	.004	0.79	0.69	0.13
Likelihood	2.86[a]	0.49	89	2.52[b]	0.61	36	2.61[b]	0.54	35	5.77	2, 150.02	.004	0.62	0.84	0.19
Experiencing	2.66[a]	0.77	90	2.25[b]	0.90	38	1.97[b]	0.65	35	10.62	2, 147.09	<.001	1.23	0.71	0.41
Positive															
Vividness	3.43	0.96	87	3.68	1.16	39	3.50	1.00	34	<1	2, 144.89	.381	0.10	0.31	0.22
Likelihood	2.87[a]	0.75	86	3.33	0.67	36	3.17[b]	0.64	34	4.42	2, 143.80	.014	0.56	0.80	0.32
Experiencing	3.19	0.86	87	3.43	0.87	37	3.24	0.90	34	1.07	2, 146.95	.345	0.08	0.35	0.30
MII															
Low mood															
Frequency	4.58	2.39	95	5.05	2.28	40	4.86	2.14	28	<1	2, 139.76	.566	0.14	0.26	0.11
Realness	6.15	1.86	75	5.71	2.32	35	5.61	1.70	23	<1	2, 121.17	.381	0.42	0.30	0.07
Compellingness	6.21	2.04	76	5.64	2.33	36	5.87	1.58	23	1.00	2, 132	.369	0.24	0.38	0.14
Demotivating	6.64	2.49	74	5.18	3.01	34	4.58	2.50	24	7.15	2, 129	.001	1.01	0.78	0.23
Anxious mood															
Frequency	4.76	2.96	76	5.26	3.02	31	6.32	2.16	19	1.75	2, 107.53	.178	0.76	0.20	0.55
Realness	6.63	1.80	57	6.75	2.07	24	6.00	2.29	19	<1	2, 97	.403	0.46	0.09	0.49
Compellingness	6.63	2.10	57	6.5	1.93	24	6.32	1.95	19	<1	2, 95.66	.831	0.21	0.08	0.13
Threatening	6.57	2.43	56	6.17	2.81	24	5.53	2.76	19	1.18	2, 96	.311	0.56	0.22	0.31
High mood															
Frequency	5.76	2.43	100	5.95	2.43	44	5.90	2.01	31	<1	2, 151.13	.845	0.07	0.10	0.03
Realness	6.74	1.71	90	6.43	1.81	40	6.55	1.35	29	<1	2, 156	.585	0.16	0.25	0.10
Compellingness	6.73	1.67	90	6.55	1.50	40	6.57	1.50	30	<1	2, 137.80	.830	0.10	0.15	0.02
Exciting	7.51	1.51	90	7.45	1.20	38	7.81	0.96	27	<1	2, 141.09	.549	0.29	0.06	0.46

BD, bipolar disorder; UD, unipolar disorder; AF, affected group; HR, high-risk group; LR, low-risk group; SUIS, Spontaneous Use of Imagery Scale; PIT, Prospective Imagery Task; MII, Mental Imagery Interview.

Different subscripts (a, b) indicate significant differences after adjusting for false discovery rate.

The sample size per group differs by outcome due to missing data or outlier removal.

was. Affected twins in remission rated finding their images during low-mood more demotivating low-risk twins ($F_{(1,69.05)} = 11.65$, $p = .001$), and also than high-risk twins ($F_{(1,106)} = 6.99$, $p = .009$), but there were no significant differences in the latter two groups ($F < 1$). For images during anxious-mood and high-mood states, there were no statistically significant overall group differences in time spent thinking in images (frequency), nor ratings of other phenomenological properties of the images (**Table 2**).

To assess whether significant group differences in emotional imagery were driven by affected twins in remission reporting higher levels of residual depressive symptoms even during remission (**Table 1**), we repeated the above analyses with statistically significant findings without participants reporting scores > 8 in HDRS (threshold for full remission) (50), but the same pattern of findings remained (data not shown).

Cognitive (Non-Emotional) Stages of Mental Imagery

Letter Corner Classification Task

The overall group difference in LCCT performance was not statistically significant for both error rates and reaction times (**Table 3**).

Mental Rotation Task

The overall group difference in MRT performance was not statistically significant, for the intercept (index of sensory-motor processing), slope (index of spatial/imagery processing), nor error rates (**Table 3**).

Secondary Analyses

Separate Bipolar Disorder/Unipolar Depression Analyses

For the analyses on the BD only (affected-BD, high-risk-BD, and low-risk), there were no overall statistically significant group differences in positive imagery (in PIT and MII) (F's < 2.54, p's > .090) or MRT performance (F's < 1.45, p's > .246). Similarly, for the analyses on the UD only (affected-UD, high-risk-UD, and low-risk), there were again no statistically significant overall difference in positive imagery (F's < 2.65, p's > .075) or MRT performance (F's < 2.07, p's > .132).

Bipolar Disorder *Vs*. Unipolar Depression Within Affected Twins

We compared BD *vs*. UD twins in remission on all our key subjective and cognitive imagery outcomes. There was only

TABLE 3 | Cognitive (non-emotional) domains of mental imagery in affected, high-risk, and low-risk monozygotic twins for affective disorders.

	Affected (BD+UD; remitted)			High-risk			Low-risk			Overall group difference			Effect size (d) of pairwise comparisons		
	M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*	*F*	*df*	*p*	*AF vs. LR*	*AF vs. HR*	*HR vs. LR*
LCCT															
Error rates	9.42	9.98	98	10.3	9.90	43	8.27	8.23	33	0.54	2,87.05	0.586	0.13	0.09	0.24
RT (msec)	12.18	5.42	98	12.09	4.45	43	10.17	3.72	33	1.68	2,106.87	0.191	0.44	0.02	0.46
MRT															
RT easy (msec)	3,152.46	551.22	92	3,187.32	459.00	45	3,369.02	60.30	31	1.84	2,110.72	0.164	0.46	0.08	0.46
RT medium (msec)	3,470.64	509.95	92	3,426.17	463.43	45	3,592.08	511.48	31	0.80	2,117.89	0.453	0.42	0.10	0.44
RT difficult (msec)	3,558.59	472.36	92	3,562.08	447.92	45	3,705.57	459.01	31	1.16	2,133.55	0.315	0.40	0.01	0.43
Intercept (msec)	2,982.37	624.59	92	3,015.37	506.15	45	3,241.45	667.87	31	1.70	2,111.26	0.187	0.48	0.08	0.49
slope	207.20	160.10	92	171.98	214.39	45	167.93	169.56	31	0.86	2,143.23	0.424	0.34	0.25	0.03
errors	24.32	14.78	92	20.49	11.22	45	24.62	11.05	31	2.13	2,100.33	0.124	0.02	0.31	0.41

BD, bipolar disorder; UD, unipolar disorder; AF, affected group; HR, high-risk group; LR, low-risk group; LCCT, Letter Corner Classification Task; MRT, Mental Rotation Task; RT, response time.

The sample size per group differs by outcome due to missing data or outlier removal.

statistically significant group difference in one outcome of the MII. Specifically, affected-BD twins in remission rated their significant image during low-mood states as more "compelling" (M = 7.06, SD = 1.73) than affected-UD twins in remission (M = 5.95, SD = 2.06; $F_{(1,74)}$ = 4.24, p = .043).

Clinical Characteristics Across the Full Sample

Across all groups, higher levels of depressive symptoms were significantly associated with i) higher IFES scores; ii) rating *negative* imagined scenarios in the PIT as more vivid, more likely to occur and accompanied with more feelings of "experiencing"; iii) rating *positive* imagined scenarios in the PIT as less likely to occur to them; and iv) reporting (in the MII) that images during low-mood states are more "demotivating". Additionally, higher levels of anxiety symptoms were significantly associated with i) higher IFES scores; and ii) rating *positive* imagined scenarios in the PIT as less likely to occur to them.

DISCUSSION

Main Findings

This large study of 204 monozygotic twins investigated—for the first time—whether mental imagery abnormalities are present in i) affected twins with affective disorders in remission and ii) twins with high familial risk for affective disorders. Regarding the first aim, we found that remitted twins with a history of affective disorders reported greater emotional impact of intrusive prospective imagery, and greater vividness, likelihood, and subjective experience of (deliberately-generated) negative prospective imagery compared with unaffected twins at either low-risk or high-risk of affective disorders. That is, affected twins are more prone to imagining the future (whether a desired holiday or a feared examination) and when they did so it felt more real and emotional. The affected twins in remission also reported less likelihood of (deliberately-generated) positive prospective imagery compared to both high-risk and low-risk twins (however, the latter result did not survive correction for multiple comparisons). In contrast, the twin groups did not differ on measures of cognitive stages (non-emotional) of mental imagery.

In relation to the second aim, we found no evidence of mental imagery abnormalities in twins with high familial risk for affective disorders but who were nevertheless not affected. Finally, mood and anxiety symptoms were significantly associated with greater emotional impact of prospective imagery across our entire sample, replicating findings that support a dimensional and transdiagnostic role of imagery abnormalities in psychopathology (32).

Theoretical Implications

Our findings extend previous work identifying abnormalities in prospective emotional mental imagery across affective disorders in the presence of significant depressive symptoms (7, 32, 33, 37). Interestingly, our pattern of results were the same for analyses conducted using a sub-sample restricting the affected group in remission to only those individuals with no residual subclinical symptomatology (HDRS scores <8; n = 89). This suggests that imagery abnormalities are not just related to residual affective symptomatology—these critically may represent a trait-related phenomenon in individuals with affective disorders. The distinction between "state" or "trait" needs to be further delineated, for example using direct comparisons of participants during remission versus during illness episodes (while acutely depressed and/or in manic/mixed episodes). While imagery-based abnormalities that are equivalent during both illness and remission are consistent with the notion of "trait" markers, those abnormalities that more pronounced during illness episodes may additionally represent "state" markers.

The association between biases in prospection and psychopathology remains understudied, although recent research suggests its potential relevance for depression (72) and anxiety (73). Our study indicates, for the first time, that individuals with a history of affective disorders continue to experience vivid intense images of *negative* future events even during long-term remission, similar to other cognitive-emotional biases including imagery of the past (27). Instead, abnormalities in *positive* prospective imagery appeared limited to *likelihood* ratings across affective disorders (although these results did not survive more stringent corrections for multiple comparisons), and did not differentiate BD *versus* UD (both in remitted states). Future replications need to confirm if the inability to experience vivid *positive* images of future events as previously reported is only prominent during illness/depressive states (63, 74).

Our findings also highlight that unlike emotional imagery, cognitive (non-emotional) imagery processes appear intact across affective disorders in remission. While we previously found some evidence of both better and worse performance on cognitive stages of imagery in a sample of mixed euthymic and depressed BD (32), the present study confirms that cognitive stages of imagery remain largely preserved in affective disorders (32). These cognitive processes rely on general executive function as well as on more specific visuospatial abilities (1). How these processes—as measured by cognitive imagery tasks—compare to other components and measures of cognition remains unclear. This is relevant as executive function in particular is often compromised in recovered individuals with affective disorders (75, 76). However, affective disorders are largely heterogeneous with regards to cognition (77, 78); for instance, affected twins in our sample did not show any cognitive deficits compared to low-risk twins (54). Answering the above question may be relevant with a view to personalizing therapeutic interventions. As examples, common cognitive therapy techniques such as reappraisal may rely on well-functioning cognition and hence be less efficacious if executive function is compromised, and likewise, imagery-based techniques could be advantageous in those with intact cognitive stages of imagery.

Abnormalities in prospective imagery were not present in high-risk twins compared to low-risk twins, indicating that these do not fulfill the criteria for an illness "endophenotype" (28). Our data are more consistent with the notion that imagery-based abnormalities reflect (neuro)cognitive markers of the disorder itself—abnormalities that are likely to play a role in increasing future relapse given their persistence in remitted states. We note that previous research has shown altered emotional mental imagery in individuals with *phenotypic* (rather than genetic/familial) risk for BD, mainly based on the presence of hypomanic-like experiences (32, 43, 69, 79). However, our study was the first to focus instead on genetic-based risk using a twin design enabled by the unique Danish registers (49). As a potential explanation for this discrepancy, maladaptive prospective emotional imagery may be associated with phenotypic characteristics of affective disorders that lie on the same dimension of clinical symptoms, such as the actual presence of dysphoric mood (47, 62) or hypomanic-like experiences (32, 43, 69, 79), but we did not measure such features in our high-risk twins. Another potential explanation is that our high-risk twins had an average higher age compared to at-risk groups from previous research. Thus it is also possible that our sample included individuals who had a familial risk but were actually "resilient" to developing affective disorders, at least in terms of mental imagery characteristics. We have previously argued that higher extroversion and lower neuroticism may mediate sensitivity to adverse events and better functioning in this high-risk sample (56), although only future longitudinal studies will be able to clarify factors determining vulnerability or resilience.

Notably, we found no evidence of differences between affective disorders categories of BD *vs*. UD. The only exception was that remitted BD twins retrospectively described their imagery at times of depressed mood as more compelling compared to remitted UD twins. This is consistent with previous findings on suicidal imagery (37), suggesting that when asking about past mental images during depressive episodes it may be important to distinguish for specific suicidal content to clarify potential phenomenological differences. We also found that greater emotional impact of prospective imagery was associated with anxiety and low mood symptoms across our whole sample. If replicated in samples with a larger number of individuals with BD, overall these results will indicate that individuals with affective disorders may share a trait-like common profile of mental imagery characteristics, in line with a most recent dimensional and transdiagnostic model of the role of emotional imagery in psychopathology (32).

Clinical Implications

If prospective emotional imagery remains abnormally enhanced after recovery from affective disorders episodes, this could represent a vulnerability factor for future relapses through their impact on emotion and mood instability. We have previously proposed that vivid intense mental images may act as an emotional amplifier and maintain mood instability (7, 29). These novel findings highlight the importance of future longitudinal studies investigating whether imagery abnormalities during remission indeed predict subsequent illness recurrence rates.

Prospection has a key functional role in individuals' daily life: we imagine future scenarios as a way to plan action, anticipate potential events and direct decision-making, manage uncertainty, and strengthen motivation toward goals (30, 31). Future imagery can also support emotion regulation, e.g., by anticipating future rewards to overcome present difficulties (80, 81). If prospection is biased in those with past affective episodes, remitted individuals will experience negative future scenarios more vividly, more likely to happen, and such intrusive images of the future will carry maladaptive emotional impact.

Finally, our findings indicate that imagery-based treatment innovation could be guided toward tertiary rather than primary prevention—at least in relation to *familial* risk. Building on previous therapy protocols (82–84) and recent experimental

studies (85), targeting prospective imagery abnormalities using imagery-based cognitive therapy techniques has potential as a brief relapse prevention intervention, in particular in patients with greater mood instability (86). Emerging work in cognitive science also suggests that simple competing tasks can dampen recurrent "flashforward" imagery by taxing working memory while holding the flashforward image in mind (15, 87). Future studies should measure change in prospective imagery characteristics after imagery-based interventions to develop novel interventions based on mechanistic hypotheses (16).

Limitations and Strengths

Several limitations should be noted in our study. First, we did not include a dizygotic twins group; hence, we could not assess the interaction between environmental and genetic influence on variance, which is preferable when investigating potential endophenotypes. Second, we did not directly compared twins at high-risk for UD *versus* at high-risk for BD. Such comparison could establish whether familial risk in imagery abnormalities is more evident in high-risk twins given a co-twin history of BD rather than UD, because of the higher heritability of BD (19) relative to UD (20). Unfortunately we had low power to run those analyses because the high-risk for BD group was very small (n = 11). Third, we did not include a full comprehensive assessment of mental imagery (40), so it is possible that biases in other imagery domains—such as trauma memory imagery (5, 14, 88) and/or reward/motivational imagery (89, 90)—are also present in remitted affective disorders and/or high-risk twins. This might be relevant to the prevalence of trauma in affective disorders (91) and of persistent anhedonic symptomatology (92), which are both associated with relapse and worse prognosis. Finally, results from our analyses comparing patients affected with UD *versus* BD (n = 84 *versus* n = 31, respectively) and from our secondary analysis should be interpreted with caution, given the small sample size of the separate BD group (n = 31 affected and n = 11 high risk, respectively).

Major strengths of our study are the large and population-based twin sample (enabling a unique design to test hypotheses regarding familial risk), twin groups well-matched on demographic variables, and the use of validated scales and tasks that allow building on previous research and future replication. Further, participants had been in long-term remission providing greater confidence that findings were not state-related (although it remains possible that imagery is also linked to states). Importantly, our findings are unlikely to be attributed to other cognitive confounders, as our groups did not differ in general cognitive function (54). Finally, to our knowledge, this was also the second study ever to combine emotional in tandem with cognitive (non-emotional) testing of imagery abnormalities in a clinical sample.

CONCLUSIONS

Our study was the first investigation of mental imagery characteristics in affective disorders using a large population-based monozygotic twin sample. For the first time, we show that abnormalities in emotional prospective imagery also persist after recovery from acute episodes, but are not present in unaffected individuals at familial risk, suggesting that imagery characteristics are unlikely to fulfill the "endophenotype" criterion. Thus, mechanistically, imagery-abnormalities in affective disorders (BD and UD) may be best conceptualized as cognitive markers of the disorders, contributing to both psychopathology maintenance and possibly future relapse. Our findings also highlight that emotional imagery phenomenology can be useable in clinical practice (93), as a hallmark of psychopathology and ongoing vulnerability. Abnormalities in prospective emotional imagery represent a promising target for mechanism-testing in treatment innovation in affective disturbances.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The study was approved by the local ethics committee (H-3-2014-003) and the Danish data protection agency (2014–331–0751). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS contributed to study design, data analysis, data interpretation, and manuscript writing. AL-Z conducted data analysis and contributed to data interpretation and manuscript writing. PT contributed to data processing, data analysis, and manuscript writing. IM conducted data collection and contributed to study design and data processing. LK and MV contributed to study design. EH contributed to study design, data interpretation, and manuscript writing. MV designed, obtained the ethical permissions, led the register linkage, and supervised together with LK the recruitment of participants and data collection. KM designed and managed the study, including data collection and processing, and contributed to manuscript writing. All authors reviewed and approved the final manuscript.

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Smartphones and Wearables as a Method for Understanding Symptom Mechanisms

Benjamin Griffin[1] *and Kate E. A. Saunders*[2,3]*

[1] Wadham College Oxford, Oxford, United Kingdom, [2] Department of Psychiatry, Oxford University, Warneford Hospital, Oxford, United Kingdom, [3] Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, United Kingdom

While psychological treatments have been shown to be effective in treating psychiatric disorders, the mechanism of their therapeutic effect is less well understood. An improved mechanistic understanding of psychiatric disorders and their treatments would enable refinement of existing interventions, and more targeted intervention and the development of new treatments. A major limitation in understanding the mechanism of effect in psychological treatments has been the challenge of capturing what happens outside of the clinical setting. The development of new digital technologies such as smartphones and wearables enables much more inter-session data to be collected. The rapid evolution of smartphones and wearable technologies, combined with the ubiquity of mobile networks means that is possible for patients to provide regular, longitudinal, and high-resolution data. This allows a previously inaccessible and untapped stream of a specific patient's behaviours, moods, activities, and thoughts to be quantified. Monitoring through such technologies may be of therapeutic value, improving self-awareness and promoting mentalization. Smartphones and wearable technologies can also be used to delivered therapies remotely. Digital technologies enable new insights to be gained into the lived experience of mental disorder enabling current treatments to be refined and personalised, as well as generating new targets for future treatment development. In this article we discuss how such technologies are improving our understanding of psychiatric disorder, informing psychological treatments before considering the future potential of such technologies. We will also consider the challenges and ethical concerns of such approaches.

Keywords: wearables, symptom monitoring, mechanism, psychological treatments, digital technology, mental health

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***Correspondence:**
Kate E. A. Saunders
kate.saunders@psych.ox.ac.uk

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INTRODUCTION

Direct clinical evidence fairly incontrovertibly demonstrates that psychological treatments are effective for the vast majority of mental health disorders, including mood (1), anxiety (2), eating (3), psychotic (4), and personality disorders (5). The diversity of such psychological approaches in treating mental conditions is vast: spanning from Freud's 'psychoanalytical theory', in which

emphasis is placed upon exploring the unconscious mind and how an individual's childhood experiences may have shaped this, to cognitive behavioural therapies (CBT), which aim to be more problem-focused and action-oriented.

However, despite these differences in the way mental health problems are conceptualised, construed, and thus treated by the different schools of psychological therapies, evidence suggests that most psychological therapies have some effectiveness in treating mental disorder. It has previously being claimed that all psychological therapies are equal (6, 7), yet a number of meta-analyses suggest that CBT may be more effective than other forms of psychological therapies (8). However, CBT's superiority does not extend to all psychiatric conditions.

This lack of clarity has led to the hypothesis that psychological treatments all work *via* "non-specific" mechanisms, an argument given more weight by the fact that the precise mechanisms by which therapies work are largely unknown. Some commentators have suggested that this "non-specific mechanism" may be better characterised as the "therapeutic alliance" between patient and practitioner, as this is one of the most consistent predictors of psychotherapy outcome (7, 9). Proponents of this theory argue that the relationship between therapist and patient is more important that the specific school of psychotherapy used, and highlight the difficulty in controlling for this in clinical trials.

Our ability to assert which therapy is most effective for a given condition is also limited by our ability to measure improvement. The highly complex and dynamic lived experience of an individual with a mental illness is often reduced to what can be easily coded and analysed in studies: crude scoring systems which provide a snapshot of symptomology on a single day, rather than a longitudinal view of function over weeks or months. Psychiatric conditions are highly heterogenous both in their aetiology and their presentation and the optimal treatment for one individual may differ significantly to that for another. However, the majority of trials present between group differences and are rarely powered to explore individual predictors of treatment response.

Recent technological advances provide investigators with a new set of tools which enable real-time monitoring and the addition of personalised outcome measures. A number of preliminary studies have demonstrated the immense power of these technologies, allowing a previously inaccessible and untapped stream of a specific patient's behaviours, moods, activities, and thoughts to be measured.

A REVOLUTION IN DATA COLLECTION

Digital technologies enable researchers to collect and analyse vast amount of naturalistic data i.e. data collected from individuals in their natural environment (10). This approach, sometimes referred to as 'digital phenotyping' (11), is defined as moment-by-moment quantification of the individual-level human phenotype in-situ using data from personal digital devices (12). Previously, data collection and treatment monitoring has been limited to being carried out in person in clinical settings, thus providing data sets of limited size and utility.

Such digital approaches provides a solution to the inherent limitations of cross-sectional self-reported data collected in a clinical setting by providing instantaneous and more objective sources of measurement. This can be utilised in the context of psychological therapies to better inform and personalise treatment, explore mechanisms, treatment concordance and provide more accurate quantification of treatment outcome.

SYMPTOM MONITORING

Symptom monitoring forms part of a number of therapies but the momentary nature of smartphone-based monitoring enables more detailed inter-session information to be collected, leading to better informed therapy sessions and provide more specific information about when in therapy positive changes begin to occur. Repeated sampling of behaviours, experiences and feeling in real time, termed ecological momentary assessment (EMA) (13) can provide insight into the temporal relationship of symptoms which may then inform subsequent therapy. The utility of EMA has already begun to be realised across a range of studies, in a variety of mental disorders. For example, prospective monitoring of individuals with post-traumatic stress disorder (PTSD) revealed that PTSD symptoms predicted subsequent anger issues, but the inverse is not true suggesting that trauma may be highly relevant to anger management (14). In panic disorder EMA has revealed the nature of the relationship between anticipatory anxiety and panic attacks supporting the underlying cognitive theories in extinction research (15). These findings have clear therapeutic implications. In bipolar disorder mood monitoring has revealed that mood instability is a far more prominent feature than previously thought (16), acting as a prodromal feature, a marker of severity and has an impact upon inter episode functioning. This not only has potential implications for the diagnostic criteria, in which mood symptoms are categorised into discreet episodes, but also how psychotherapies may be best designed to treat such patients.

PASSIVE DATA COLLECTION

While rating symptom scores throughout the day are extremely valuable it relies on individuals completing their ratings and assumes their self-appraisal to be accurate. It has been long established that symptom reporting can be a therapeutic intervention in itself, but patients can become fatigued with answering the same questions on a regular basis and there are concerns that active monitoring can act as a reminder of illness. The temporal resolution is inherently limited to the frequency of prompts a patient is prepared to tolerate. In addition when people become unwell often stop reporting their symptoms or do so in a less reliable manner making the interpretation of the data challenging. One of the significant advantages of new

smartphone and wearable technologies is their ability to collect passive data streams. Passive data is information that is collected automatically without the participant having to do anything. Passive monitoring can take many forms, with one of the most promising of these being the ability to quantify human-computer interactions. This not limited to measuring just *what* is being done, but rather *where, when,* and *how* it is being done, for example how we interact with mobile phones. A recent small-scale study demonstrated subtle aspects of typing and scrolling such as the latency between space and character or the interval between scroll and click can be used as surrogates for affective states and cognitive traits, (17). Aspects of phone use such as length and number of outgoing phone calls, the number of outgoing text messages per day (18), the variability in geolocation have all been shown to correlate with severity of mood symptoms (19).

Passive data is continuous, often multimodal in nature and inherently ecologically valid while minimising the burden on patients. In the context of psychological treatments this technology provides a platform for testing different psychological theories. For example theories that relate to interpersonal relationships or emotional dynamics often require much greater temporal resolution that self-report is able to provide. Koval and Kuppens (20) have proposed the theory of emotional inertia where the autocorrelation of an individual's emotions over time predict depressive symptoms. The use of continuous, high frequency passive data allows such theories to be tested outside of laboratory settings. In therapies that have significant behavioural components passive data collection can not only measure compliance but also the temporal relationships between behavioural and other symptoms.

Passive data may also enable treatments to be more accurately targeted both temporally and situationally. Such digital approaches raise the possibility of technologically informed individualisation. Through analysing the data stream of one patient, it may be possible to algorithmically predict future events based on the past: for example, in bipolar disorder where the notion of idiosyncratic 'relapse signatures' has begun to be characterised (21), it is conceivable that such prodromal features could be detected digitally. Moreover, these insights not only inform when intervention may best be delivered, but act as a psychoeducation tool enabling patients to develop a better understanding of their disorder. Digital CBT interventions such as Sleepio are already integrating data streamed from wearable devices into their interventions thus providing intervention which is based this objectively collected data.

Passive data collection has also extended to the use of optical sensors mounted in homes or clinical settings. These sensors can detect patient's location, activities, and vital signs (heart rate and respiratory rate) and have been demonstrated to be well tolerated by patients (22). Such digital observational systems are currently confined to inpatient environments but could be used in a range of clinical or home settings to monitor a range of patient behaviours including real-time measurement of group process and interpersonal dynamics.

CHALLENGES AND CONTROVERSIES

While such technologies clearly represent a huge opportunity they also present complex practical and ethical issues to those working in this area.

New technologies undoubtedly allow us to collect data in much greater quantities, at higher temporal resolution across multiple different modalities. There are concerns that data collection in this area is often not 'hypothesis driven': large amounts of data are collected over a long amount of time without researchers having anything specific to test. Vast stores of data may accumulate over many years before analysis and subsequent use might occur. The ways in which data may be used in the future appear almost infinite: this presents a problem in the fact it is not possible to consent those using such technologies currently as to what their data may be used for in time to come. Such large volumes of data present a huge analytic challenge as for any of these technological advances to be realised the data they provide must be valid, interpretable and reliable. Missing data is a common challenge especially in self-reported data. Data may be missing for multiple technical (for example power cuts, battery failure) practical or clinical reasons. This can pose a challenge when analysing the data as the methods for dealing with missing data may have a significant impact upon the findings. If data is missing at random and it may seem reasonable to use imputation (the process of replacing missing data with a substituted value), but if the missing data conveys information about a clinical state (or both), any attempt to impute data may in fact lead to the loss of data. Knowing which of these respective approaches is correct for any given data set is almost impossible.

Analysing large complex data sets often requires techniques that cross traditional disciplinary divides drawing on approaches from engineering, maths and computer science. These analytic approaches are key to the viability of using digital data to provide meaningful within subject outputs. Such approaches are generally not well understood by clinical staff or easily interpretable and are likely to require close collaboration and changes to training of clinical staff.

The regular use of smartphones or other wearable devices also requires patients to keep devices charged and turned on. They need to be able to access network connections. Sensor data uses significant amounts of battery life which may lead to data collection being switched off. Sensors differ significantly between devices and operating systems making the accurate quantification and comparison of data between individuals challenging.

There are risks surrounding data security and patient confidentiality. This is well exemplified by research carried out by Nicholas et al., reporting on mobile apps for bipolar disorder: none of the symptom apps identified by the group had been subject to rigorous research or cited published material, and only 22% had a privacy policy (23). For apps and wearable devices to be acceptable to patients there needs to be clear and rigorous mechanisms to uphold privacy. Efforts are now being made to mitigate such risks: the Department of Health and Social Care has recently published a code of conduct for data-driven health and care technology, outlining 10 key principles for safe and effective digital innovations, and detailing 5 government

commitments aiming to ensure that the health care system is ready and able to safely adopt innovations in technology on a large scale. The Medicines and Healthcare products Regulatory Agency (MHRA) has recently issued updated guidance to help identify whether software and health apps are medical devices and the National Institute for Health Research (NIHR) is now offering regulatory advice for those seeking to develop novel medical technologies.

The acceptability of digital data collection to patients is central to the uptake of such approaches in research and clinical settings. A number studies, including a multi-site collaborative study which involved patients with a range of disorders, suggest that the use of digital technologies is highly acceptable to patients, and levels of compliance appear to relatively high (24, 25) . However, concerns have been raised regarding the propensity for individuals to develop preoccupation and paranoia with their continual monitoring (26). A large follow-up study of a cohort of bipolar patients found that 20% of those offered online mood monitoring declined citing concerns that longitudinal monitoring could adversely affect mood (27).

These somewhat disparate findings may be explained by the fact that the studies in which use of digital technologies was more positively appraised patients received face to face training from the investigators, compared to the use of post and email to train patients in the other studies. This suggests that in order to maximise the acceptability of digital technologies to patients, efforts should be made to optimise levels of training and support offered to them.

There is evidence linking increased use of smartphones to decreased psychological wellbeing in adolescents. When controlling for other factors, researchers found that increased mobile phone use was linked to subsequent decline in well-being, while those adolescents spending the least amount of time on electronic communications reported higher levels of well-being (28). This ties into research indicating that remote monitoring may increase symptoms of anxiety and mental distress. While these studies are far from conclusive, and only considered very specific cohorts so may not be more widely applicable to psychiatric patients, it is reasonable to question whether encouraging patients to spend more time on their mobile phones may do more harm than good in some cases.

CONCLUSION

The use of remote monitoring using digital technologies in psychiatry has expanded exponentially in recent years, providing researchers and clinicians with a hugely powerful and diverse set of new tools to explore and treat psychiatric disease. Unprecedented quantities and types of data from naturalistic settings promises to revolutionise our understanding of symptoms in this currently poorly understood area of medicine. This will enable the more rigorous scrutiny of the mechanism of action of existing psychological treatments as well as the generation of new psychological treatment targets. Whilst the impact of digital technologies is likely to be positive, a number of ethical and practical issues have to be considered. Actively seeking to involve patients in the development of such technologies, and providing adequate training and support for those using the devices and apps is likely to be key to the success of digital approaches. Greater effort should be made to understand the wider implications of the use of such technologies in psychiatry, with the aim of balancing the clinical and research possibilities against the health of patients, and the safety of their data.

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Under the Hood: Using Computational Psychiatry to Make Psychological Therapies More Mechanism-Focused

Akshay Nair[1], *Robb B. Rutledge*[2,3] *and Liam Mason*[2,3,4]*

[1] Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, London, United Kingdom, [2] Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Berlin, Germany, [3] Wellcome Centre for Human Neuroimaging, University College London, London, United Kingdom, [4] Research Department of Clinical, Educational and Health Psychology, University College London, London, United Kingdom

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Edited by:
Cynthia H. Y. Fu,
University of East London,
United Kingdom

Reviewed by:
Vyv Huddy,
University of Sheffield,
United Kingdom
Warren Mansell,
University of Manchester,
United Kingdom
Anubhuti Dubey,
Deen Dayal Upadhyay Gorakhpur
University, India

***Correspondence:**
Liam Mason
l.mason@ucl.ac.uk

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Psychological therapies, such as CBT, are an important part of the treatment of a range of psychiatric disorders such as depression and anxiety. There is a growing desire to understand the mechanisms by which such therapies effect change so as to improve treatment outcomes. Here we argue that adopting a computational framework may be one such approach. Computational psychiatry aims to provide a theoretical framework for moving between higher-level psychological states (like emotions, decisions and beliefs) to neural circuits, by modeling these constructs mathematically. These models are explicit hypotheses that contain quantifiable variables and parameters derived from each individual's behavior. This approach has two advantages. Firstly, some of the variables described by these models appears to reflect the neural activity of specific brain regions. Secondly, the parameters estimated by these models may offer a unique description of a patient's symptoms which can be used to both tailor therapy and track its effect. In doing so this approach may offer some additional granularity in understanding how psychological therapies, such as CBT, are working. Although this field shows significant promise, we also highlight several of the key hurdles that must first be overcome before clinical translation of computational insights can be realized.

Keywords: psychological therapies, decision-making, computational psychiatry, computational neuroscience, CBT (cognitive-behavioral therapy), reinforcement learning (RL), mechanisms, reward (healthcare)

INTRODUCTION

There is growing recognition that, to move forward, the field of psychological therapy needs to return to its scientific roots and become more mechanism focused. A Lancet commission for improving psychological therapies urged greater synergy between basic and clinical research (1). In this paper, we argue that considering psychological therapies from a computational perspective may be one such approach to achieve this aim.

The emerging field of computational psychiatry aims to provide a theoretical framework for moving between higher-level psychological states (including emotions, decisions and beliefs) to neural circuits, by modeling these constructs mathematically (2, 3). Here, we do not cover the breath of research in computational psychiatry and direct interested readers to other recent

reviews (3, 4). Instead, the focus of this piece is how a computational framework may translate to psychological therapies by allowing us to get closer to the generating mechanisms of symptoms and distress (5, 6). For a consideration of how these frameworks might provide insight into the generating and maintaining processes targeted by psychological therapies, the reader is referred to (5). In this article, we primarily focus on the application of "reinforcement learning" models (7) to understanding and evaluating cognitive behavior therapy (CBT) specifically. There are a wide range of psychological treatment modalities, such as psychodynamic therapy (8) and humanistic (9) approaches. There are also many approaches derived from or compatible with computational modeling, including active inference (10) and perceptual control theory (PCT) (11, 12) which make different predictions about the relationship between internal states and behavior [for example in PCT, the control of sensory input through behavior, see (11)]. It is beyond the scope of this article to cover them all, and we focus on reinforcement learning and CBT as examples, as two of the most widespread frameworks. We do not necessarily advocate for these two frameworks above others; rather, we use them as salient examples of how computational theory can help us better to understand how psychological therapy works. We also discuss some of the challenges that currently limit the translation of computational psychiatry into clinical practice.

What Is Computational Psychiatry?

A central goal of CBT is to support patients in moving toward their goals, which will typically involve helping patients to adapt their beliefs and behavior to their current environment (13). Put in computational terms, such therapies, in effect, alter the mapping between *states* the person is in, for example an anxiety-provoking situation, like giving a presentation, and *actions*, such as staying or escaping. In computational terms, this mapping between states and actions is known as the *policy* (7). By helping patients adapt their beliefs and behavior, psychological therapies can be understood as helping patients adopt new policies. For example, consider a musician with depression reporting that they now get less pleasure (or *reward*) from a past-time that they used to enjoy, such as playing the guitar, and so have stopped entirely. Here, a possible psychological mechanism maintaining their depression would be behavioral avoidance (14). That is, a lack of positive reinforcement from their environment and/or negative reinforcement of the avoidant behavior (e.g., not playing the guitar serves to avoid experiencing negative emotions of feeling upset and ashamed whenever they don't play the guitar perfectly).

Algorithmically, this *prediction error*, the difference between reward and expectation, is used to update the "value" of that action for the future. In this case, the *value* of playing the guitar will reduce, so that in the future when trying to decide what to do, it is much less likely that playing guitar will be chosen

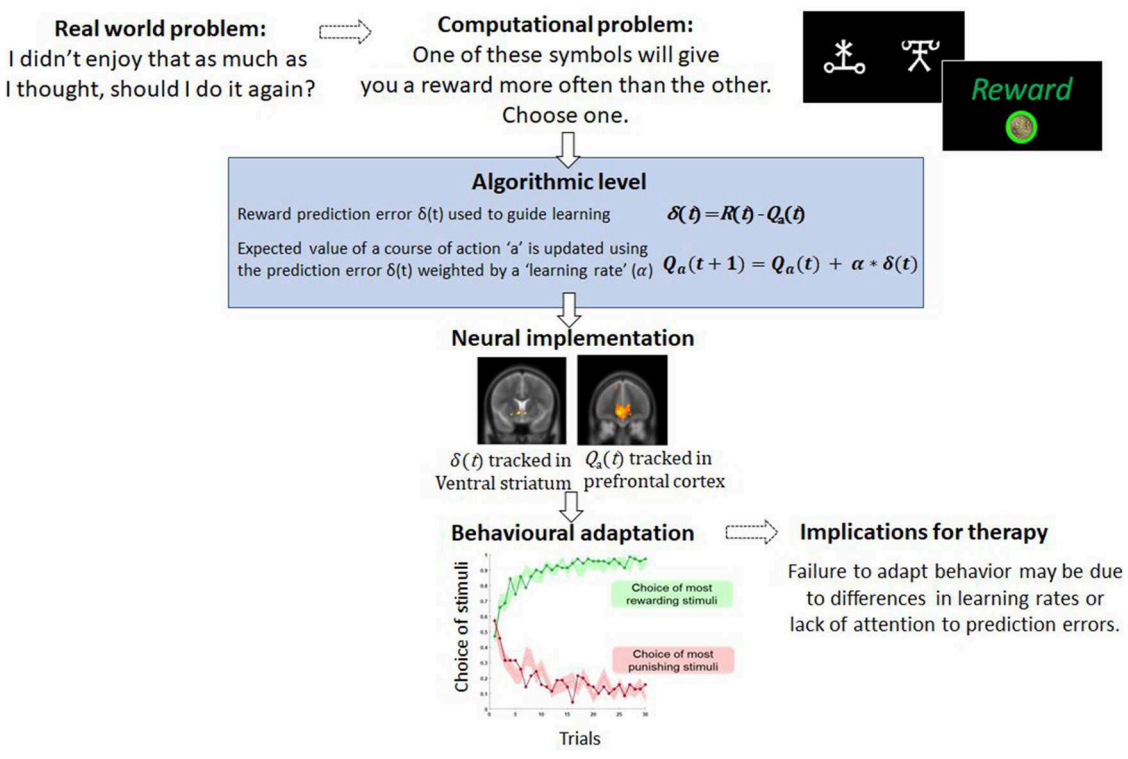

FIGURE 1 | An example of a computational problem—learning which actions are the most and least rewarding. In typical tasks, participants choose between stimuli which differ in terms of reward probabilities. Through trial and error participants learn to choose and to avoid the best and worst options, respectively. This type of behavior is well-captured by simple computational models like the one described and variables from these models, such as the prediction error, correlated with brain activity. For therapy, failure to learn from rewarding or punishing experiences may limit the capacity to change behavior.

because the expected value has fallen (**Figure 1**). As such, the patient's *policy* has changed. Successful behavioral therapy would seek to reverse this. Within computational models, this updating is typically controlled by a parameter known as the *learning rate*. Variability in the learning rate parameter reflects how sharply the value of actions, such as choosing to play guitar, are changed by recent prediction errors.

Can Computational Parameters Be Used to Measure Change During Psychological Therapy?

If CBT results in changes in policy, then computational parameters such as the learning rate, should determine the rate of this change and therefore, may be an early predictor of treatment response. Indeed, if parameters control a process that generates or maintains psychiatric symptoms, then changes to these parameters could precede and mediate subsequent improvement of those symptoms. An analog from pharmacotherapy is the finding that the clinical benefit of antidepressant medication, which is typically on the order of weeks (15), may actually be preceded by a normalizing effect on the neural processing of negative emotional information that is evident on the order of hours (16). As such, change in computational model parameters may also serve as useful secondary outcomes for evaluating the effectiveness of psychological therapy. For example, in patients with anxiety who have measurable differences in learning rates as compared to controls (17), change in these parameters may suggest successful psychological intervention even if symptoms have not yet reached remission. This is analogous to the use of biomarkers in clinical trials being used as secondary outcomes—for example, changes in amyloid-beta measures in clinical trials for Alzheimer dementia may suggest possible treatment efficacy even if no change is seen in cognitive scores (18). It has previously been proposed that outcomes in psychological therapy could be formally modeled, using *dynamic systems theory*, for example (19, 20). As compared to these proposals, computational modeling parameters from reinforcement learning models would serves to model the underlying computational process driving change rather than the complex dynamics of psychotherapy. This is, of course, dependent on identifying computational differences that track the relevant state or trait features that psychological therapy is aiming to target. From pharmacology studies it can be shown than administering drugs that act on dopamine and serotonin neurotransmitter systems, for example, can alter fitted computational parameters in behavioral tasks (21, 22). The same may be true for efficacious psychological therapies.

The computational approach is also appealing because variables derived from algorithmic models have been shown to be tracked by the brain (23). This is valuable because neurobiological measures provide objective measures of the processes that generate behavior which are often not amenable to accurate self-report (1). Moreover, there is amassing empirical evidence that psychological therapy leads to reorganization at the neural level. For example, longitudinal functional MRI studies of CBT identify a strengthening of connections between prefrontal cortex and limbic regions [consistent with contextualizing and regulating emotion and potential threat (24, 25), and that the extent of these CBT-led changes may predict the degree of remission experienced several years post-therapy (26)]. In tasks that involve learning and the updating of beliefs and behavior, *reinforcement learning* algorithms not only account for behavior but also predict regional brain activity. Numerous fMRI studies have reported that the *prediction error* signal, described above, correlates with the activity in the ventral striatum and frontal cortices in fMRI studies of instrumental learning (23) (**Figure 1**), and there is recent evidence that these signals predict response to CBT (27). The expected value of a chosen option has also been shown to correlate with activity in the medial prefrontal cortex (28). Outside of learning tasks, other models which consider costs show that effort and net-value may be coded in different brain regions such as the cingulate cortex (29). If these computational parameters and variables from models are associated with psychological recovery, this approach may offer deeper localization of the therapy effects. Furthermore, recent movements in CBT have focused attention away from disorder-specific interventions to underlying psychological processes appearing across multiple disorders (30, 31). This newer approach is arguably a better fit with computational modeling of brain and behavior as the role of computational parameters in determining decision-making or behavior is not limited by diagnosis. Largely in this article we have focused on parameters that change with clinical state. However, variance in these parameters when patients are well may be a readout of underlying processes which put patients at risk of mental health difficulties.

Can Computational Parameters Inform Formulation and Tailor Delivery of Psychological Therapy?

Computational models make several testable predictions relevant to understanding the variance in the efficacy of psychological therapies. Firstly, change techniques will be less effective for those patients who struggle to update the value of actions based on new evidence (i.e., those with lower learning rates for that target belief or behavior). Secondly, more targeted approaches that increase learning rates for therapy-guided action-outcome pairs may increase the effectiveness of interventions (by fostering new learning and updating policies). A key factor determining the success of cognitive-behavioral techniques such as behavioral experiments, in which patients test out what happens when in a feared situation, is whether their prediction about what will happen has been clearly operationalized (32). In the current framework, this step ensures that the prediction error generated if the outcome differs from what was feared is then optimally attended to and utilized to update future expectations about similar situations. Indeed, attention to prediction errors has been shown to be a key process for efficient learning and belief updating (33). Therefore, a third prediction would be that adding preparatory work that promotes attention to prediction errors will increase the effectiveness of the separate learning-based intervention. Behavioral interventions for depression, for example, assume that low mood is maintained by a

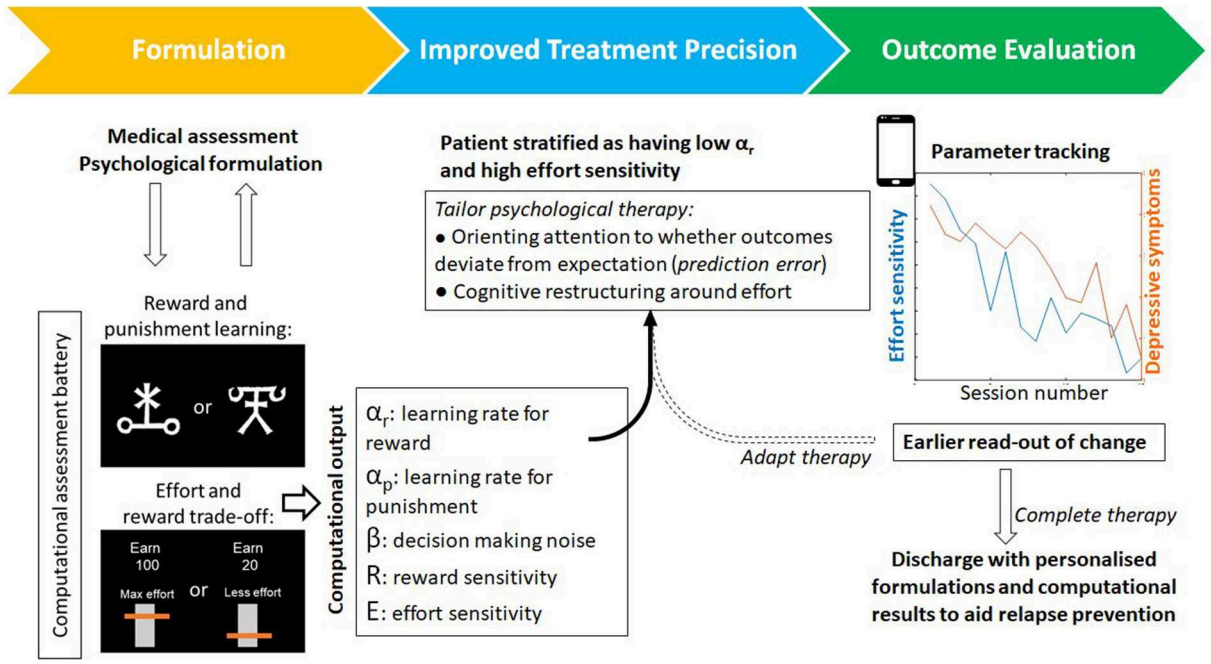

FIGURE 2 | An example of a patient journey through psychological therapy that incorporates computational assessments. Alongside psychological formulation, task-based assessments output individual parameters for a range of computational processes–such as reward learning or effort discounting. From this analysis, a tailored computational profile could be used to tailor components of therapy (for example attention and learning during behavioral activation versus cognitive restructuring of beliefs around effort). These computational parameters provide objective markers for evaluating change and, by virtue of being closer to the underlying mechanisms that generate or maintain symptoms, may provide an earlier readout of change that precedes symptom improvement. Tasks exist in adapted forms for use online or on smart devices that may also improve patient access and engagement.

reduction in rewarding experiences in a person's life and aim to bring the client back into contact with meaningful rewarding experiences. An important component involves the client making formal predictions about how enjoyable, or unenjoyable, an activity will be and re-rating that with the actual level of enjoyment experienced (14). This process increases the chances that a prediction error is computed and utilized to update beliefs.

Computational work also suggests that psychological therapies could be tailored to individual patients. Recent work has shown that prediction errors come in many shapes and sizes. An action could also vary not only in the amount of reward it yields but in the estimated effort, or other costs, needed to obtain reward. There is evidence that estimations about any of these aspects may go awry when someone is depressed (34). Behavioral activation often involves the client quantifying how rewarding an activity will be (reward predictions), but recent work shows that the brain also computes *effort* prediction errors used to learn the costs associated with different states (35). These effort prediction errors could also be harnessed for the purpose of learning and updating as described above (**Figure 2**). As with reward prediction errors, learning rate may also vary between patients. Patients could therefore be stratified therefore not only on reward-based parameters but differences in cost-based parameters like effort sensitivity and effort learning rates. These parameters could be used to tailor the cognitive-behavioral change techniques that are deployed.

RECOMMENDATIONS AND FUTURE DIRECTIONS

Although this approach holds significant promise, we lack concrete examples of computational psychological therapy. There is promising work for example in anxiety, implicating the failure to adaptively modulate learning rate (36) that nonetheless currently falls short of clinical translation. The field also faces a number of hurdles which limit its application into clinical practice—these include reproducibility, generalizability, and scalability (**Box 1**). Computational parameters are estimated by fitting a model to behavior generated in bespoke behavioral tasks. In its nascent state, much computational research is currently focused on expanding current knowledge often with novel tasks and new models of behavior. For computational modeling to be useful in clinical practice, equal focus should be placed on pragmatic concerns such as generating reproducible findings and increasing the test-retest reliability of task performance and parameter estimation. For computational parameters to act as secondary outcomes in therapeutic trials they will be required to show stability over time in relevant control groups. Test-retest reliability of computational parameters appears currently modest (38), reducing the power of clinical trials where they could offer greater granularity to detect changes in cognitions and behavior that are relevant to treatment efficacy. Furthermore, the use of bespoke tasks in individual studies limits interpretability and evidence synthesis (including meta-analysis across studies).

BOX 1 | Road blocks for integrating computational approaches to understanding psychological therapy

1. Reliability. Whilst computational model parameters show promise, their test-retest reliability for specific tasks often remains to be established. In order to reap the benefits of more objective and direct measures of neuro-computational processes, extensive validation of the stability of tasks and model parameters over time is needed. Only computational parameters that show good test-retest reliability can they be used to track clinical state and evaluate the effectiveness of interventions.

2. Generalizability. Even once stable task measures are derived, a major gap to be filled is to confirm that they are predictive of real-life phenomena. For example, model parameters purporting to measure mood instability within an experimental setting should predict real-life mood fluctuations experienced by patients (for example via experience sampling). A second requirement is that if change in these task-based parameters is effected by some intervention, it should translate to benefits in real-life symptoms and functioning. This is analogous to the challenges faced by approaches involving cognitive training (37).

3. Scalable and easy to implement. Unlike other biomarker approaches including those which require neuroimaging technology, computational approaches provide inexpensive and practical measures that are collected behaviorally but grounded in neurobiology. They lend themselves to convenient online and smartphone-based data collection. This makes them more practical and far less expensive than fMRI for the purpose of patient stratification, treatment selection and other clinical decision-making. They also lend themselves to longitudinal "self-assessment" for the purpose of symptom monitoring and/or treatment evaluation.

Avoiding this confusion is especially important when seeking to synthesize effect of a treatment on an outcome, such as the effect of CBT for anxiety on the learning rate in volatile environments.

Second, although parameters from models govern behavior, the degree to which they predict behavior outside of carefully controlled experimental conditions remains to be robustly established. Ideally, computational model parameters should capture real-life phenomena in ecological settings, and changes seen in controlled settings must generalize between the two. There does not appear to be good support for this at present (39). Others have argued the need for ecologically valid tasks and models (40) and this argument becomes stronger when wanting to demonstrate functional improvement following psychological therapy. Returning to the example of the depressed patient who no longer enjoys playing the guitar, computational parameters from a reward task should ideally predict not only abstract task performance but the patient's ability to return to their hobbies as they find them more enjoyable. Third, achieving this may also benefit from data collection in real-life settings, since they are closer to the environment which neural circuits should be tuned to and where symptoms arise. As alluded to above, unlike other biomarker approaches which require neuroimaging technology or biofluids, computational approaches can provide inexpensive and practical measures that are collected behaviorally but grounded in the underlying neurobiology. They lend themselves to convenient online and smartphone-based data collection. This makes them more practical and far less expensive than fMRI for the purpose of patient stratification, treatment selection and other clinical decision-making. They also lend themselves to longitudinal "self-assessment" for the purpose of symptom monitoring and treatment evaluation. There are already notable examples of the scalability of this approach for objective smartphone-based measurements of mood and decision-making, including in the clinical population (2, 41, 42). This approach also allows task-derived parameters to be validated alongside the real-life phenomena they supposedly capture, for example by tracking mood and associated measures of activity such as step count (43).

In summary, we argue that the inclusion of the computational characterization of behavior for patients undergoing psychological therapies offers a number of unique advances. Firstly, it is a principled theoretical framework to bridge psychological constructs with neural circuitry and function via mathematical models of cognitive processes. These models are explicit testable hypotheses with quantifiable parameters which govern individual differences in learning and behavior. As such, these models can be used to assess the impact of psychological processes on deeper processes such as learning. Finally, parameters from computational models may act as secondary outcome measures predicting psychological recovery that may precede behavioral or changes in symptom levels (**Figure 2**). There has been much recent excitement about the possibility of neuroimaging biomarkers for patient stratification (44). It remains to be seen whether computational biomarkers will achieve the same level of performance as neuroimaging biomarkers, but given that the costs can be more than a 100-fold lower, computational approaches hold considerable promise to improve psychological therapies. There remain a number of challenges. In order to be beneficial to treatment trials, computational tasks should be standardized and their parameter estimates should be stable in the absence of intervention and predictive of real-world behavior. If there is sufficient appetite from practitioners and patients, to adopt computational frameworks, we are optimistic that these limitations will be addressed and adopting a computational approach to the study of psychological therapies will allow us to peer under the hood and to improve our therapies for patients.

AUTHOR CONTRIBUTIONS

LM and AN contributed the conceptual aspects of the paper. All authors contributed to writing the manuscript.

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Development and Validation of Fear of Relapse Scale for Relapsing-Remitting Multiple Sclerosis: Understanding Stressors in Patients

Ali Khatibi[1,2*], *Nahid Moradi*[3], *Naghmeh Rahbari*[4], *Taranom Salehi*[5] *and Mohsen Dehghani*[6,7]

[1] Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, United Kingdom, [2] Centre for Human Brain Health, University of Birmingham, Birmingham, United Kingdom, [3] Department of Neurology, Royal Melbourne Hospital, Melbourne, VIC, Australia, [4] Department of Cognitive Psychology, Institute for Cognitive Science Studies, Tehran, Iran, [5] Department of Psychology, Allameh Tabatabaei University, Tehran, Iran, [6] Department of Psychology, Shahid Beheshti University, Tehran, Iran, [7] Neuroepidemiology Unit, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia

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***Correspondence:**
Ali Khatibi
ali.khatibi@gmail.com

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Chronic diseases are associated with patients' long-term stress and development of fear to things related to the source of stress. Better management of a patients' condition requires investigation of the underlying mechanisms that contribute to the process of development of chronic stress. Multiple Sclerosis (MS) is a debilitating chronic disease in most cases diagnosed after a relapse and characterized by the periodic occurrence of relapses in most patients. Due to the unpredictable course of the disease and relapses, patients with Relapsing-Remitting MS (RRMS) may deal with the stress of anticipation of relapse and its unpredictable consequences. The role of relapses and related stress on patients' quality of life has not been previously investigated. This study is the first effort to develop a self-report measure of Fear of Relapse (FoR) in patients with RRMS. Thirty-one items were extracted from in-depth clinical interviews with 33 RRMS patients to develop the preliminary version of the scale. Subsequently, 168 RRMS patients completed the questionnaire, the Intolerance of Uncertainty Scale (IUS) and Depression, Anxiety, and Stress Scale (DASS). Fifty-one patients completed the scale one more time a month later. Factor analysis revealed three components, and five items failed to load on any of them. To test the FoR's independence from similar measures, responses to 26 items were pooled once with DASS items and once with IUS items, and each time were subjected to confirmatory factor analysis (two-component solution). Despite significant correlations between FoR, DASS, and IUS Independent loadings of items belonging to FoR and DASS, and FoR and IUS revealed independence and unique contribution of FoR to the evaluation of patients. Cronbach's alpha for the 26-item version was 0.92. Test-retest reliability for total score was equal to 0.74. These findings provide preliminary evidence of the validity and reliability of the measure. This scale can help researchers and clinicians to have a more comprehensive understanding of patients'

experience with the uncertain nature of MS, which is necessary for future efforts to address this stressor by targeting the underlying mechanism.

Keywords: fear, relapse, scale development, psychometric properties, Relapsing-Remitting multiple sclerosis

INTRODUCTION

Multiple sclerosis is a chronic and potentially debilitating disease of the nervous system that affects people of all ages. Early symptoms vary and may depend on one's age, life history, and other factors. Diagnosis normally follows the first major occurrence of sub-acute neurological symptoms, which include but are not limited to vision problems, sensory-motor deficits, fatigue, balance problems, and dizziness. The progress of the disease depends on many factors based on which the disease phenotype can be divided into three subgroups, Relapsing-Remitting MS (RRMS), Secondary-Progressive MS (SPMS), and Primary-Progressive MS (PPMS). The course of the disease is unpredictable for individuals, but the majority of patients manifest the relapsing phenotype (85% RRMS) (1). The relapses emerge as neurological events, which may be similar to the first attack after which the disease was diagnosed, or they might be completely different as new areas of the nervous system become involved. The underlying mechanism in the relapsing phenotype is the active inflammation and subsequent demyelination in the Central Nervous System (CNS). These relapses have short and long-term consequences and might lead to the accumulation of disability.

Many previous studies have shown that anxiety is an inseparable part of life in patients with chronic diseases (2). Fear is at the core of anxious thought of patients with chronic diseases, and the source of fear depends on the underlying condition. For example, in chronic pain, fear of pain is due to the patient's expectations about the influence of pain on his/her personal and social life and how long-term pain causes disability in both (3). Fear of progression has been found to be the pillar of the anxiety problems of patients suffering from chronic diseases like cancer and diabetes mellitus (4–6). A previous effort to develop a tool for measuring fear of progression in chronically ill patients resulted in FoP-Q, which has been shown to have proper psychometric properties (5).

A source of anxiety in the relapsing stages of multiple sclerosis is the relapse itself. Patients diagnosed with these phenotypes do not know when they might have their next relapse and do not have any estimation about the severity of the relapse and its consequences. Generally, it is well-accepted that a new relapse is a sign of disease activity and has its implications such as treatment failure or accumulation of disability. It has also been suggested that fear of progression (as an emotional response) is related to the depression observed in patients with MS while it is not correlated with gender, age, disease duration, and the stage of the disease (7).

Individual prognosis differs among patients with MS. This diversity is partly related to the phenotype and the disease duration, but these alone fail to explain the observed variation. It is important to realize that each MS phenotype is characterized by specific complications and stressors, albeit the fact that demyelination in the CNS might be present throughout the course (8). Any tool that wants to give a clear image in such a clinically diverse disease course must consider these differing stressors. Existing self-report measures describing the psychological impacts of MS on patients are limited in this regard. It has been suggested that both psychological and pharmaceutical interventions are necessary to improve the quality of life in patients with MS (9). The measures that can assess the fear related to the disease activity and the relapses are paramount as they enable evaluating the efficiency of the proposed interventions. We firstly aimed to develop a new tool to measure the fear of relapse in patients with RRMS. Secondly, we aimed to investigate the psychometric properties of this measure in an independent sample of patients.

METHOD

Diagnosis of MS in this study is done by a neurologist and based on the 2010 revision of McDonald Criteria (10).

Interviews and Item Extraction

A semi-structured in-depth interview was conducted with 33 (18 females, age between 24–47 years, mean age = 33.18 ± 6.2 years; disease duration between 3 and 8 years, mean diseases duration = 6.71 ± 3.3 years) patients with RRMS. All the interviews were conducted by the same person (N.R.). Patients were recruited from Sina specialized MS research and treatment center, Tehran, Iran. For all patients, Persian was their native language, and they had received their diagnosis in the previous five years. They were all receiving disease-modifying treatments. Expanded Disability Status Scale score for all these patients was below 4. The study was approved by the ethics committee of the department of psychology at Shahid Beheshti University, and all subjects gave written consent prior to their participation.

The interview was based on pre-selected questions in four main domains: (i) demographics and daily life experiences and difficulties, (ii) cognitive problems, (iii) psychological problems, (iv) social challenges. The interviews took 60 min at most. The sessions were audio-recorded and transcripted afterward and ATLAS.TI-6 was used for the organization of the interview material.

A number of keywords that the literature suggested for individuals' fear of relapse in MS were selected. This list included: physical difficulties, stress, anxiety, relapse, hospitalization, disease progress, fear, worries, and health problems. A total number of 156 statements were found to

contain one or more of these keywords. The content of all 156 items was reviewed by three independent experts and those with similar statements, unclear complaints, and non-relevant content were removed and summarized. The final list contained 31 items judged by their clarity, difficulty in understanding, and relevance. Each item described the patient's thoughts about symptoms that could be associated with relapse or its consequences. A patient would be asked to mention the degree to which these thoughts came to his/her mind on a five-point Likert scale (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always). The pre-final version of the scale was presented to 10 patients, and their understanding of each item was discussed. We also checked the items with neurologists with expertise in MS and also with psychologists with a focus on the treatment of patients with chronic diseases. As a result, the wording of a few items was adjusted to increase the understandability of them.

An English translation of items is provided in the tables in this article. Items were translated from Persian to English by a bilingual expert, and then back-translated from English to Persian by an independent, experienced translator. Items of the original Persian version and the back-translated items were compared, and the translation of a few items was adjusted accordingly.

Psychometric Evaluation

Participants

A total number of 168 patients with RRMS (142 females; age 17–57 years; mean = 32.65 ± 8.2) were recruited from multiple centers (Golbooteh Omid charity center, Firoozgar hospital, Sina MS research center) in Tehran, Iran, through convenience sampling method. The duration of the disease (since the initial diagnosis by a specialist) was between 0.5 and 5 years (mean = 3.19 ± 1.5) and the patients experienced between 1 and 9 relapses (mean = 3.19 ± 2.2). The last major relapse that resulted in receiving corticosteroid treatment was between 1 and 37 months ago (mean = 12.42 ± 10.6). These patients received either a paper version of the questionnaire or a link to the online version. There was no difference in the outcome of self-report measures and demographics between the groups that completed the paper or the online version. The study was approved by the ethics committee of the Department of Psychology at Shahid Beheshti University and participants had given informed consent prior to participation. For participants younger than 18 years consent was obtained from one of their parents.

Other Self-Report Measures

The following measures have consistently used in the literature of research on patients with chronic disease to capture the general anxiety and anxiety of an unpredictable future. We included them to test the construct validity of our measure.

Depression Anxiety Stress Scale (DASS-21)

DASS-21 (11) is a self-report measure of depression, anxiety, and stress among clinical and nonclinical populations and is reported to have good to excellent psychometric properties in different settings and populations (12, 13). Each item comprises a statement about feelings and experiences that the reader had to select to what degree it applied to them in the past week on a four-point Likert scale (0 = Did not apply to me at all; 3 = Applied to me very much, or most of the time). This measure and the 42 item variant has been translated to Persian and is widely used in different studies and has shown good to excellent psychometric properties [Cronbach's alpha >0.8; (14, 15)].

Intolerance of Uncertainty (IUS-27)

IUS-27 (16) is a self-report measure, with 17 items describing people's reactions to uncertainties in life. Subjects have to rate each item on a five-point Likert scale (1 = Not at all characteristic of me; 5 = Entirely characteristic of me). This measure is suggested to capture the fear of the unknown and anxiety related to that and is proved to have good psychometric properties (17). This measure has a two-factor structure that is also considered in scoring: a factor that express unfairness of beliefs related to the uncertainty about future and another factor with items about the behavioral and self-referent implications of uncertainty. The Persian version of this scale is widely used in different settings and is showed to have good psychometric properties (internal reliability = 0.88) (18).

Procedure

After receiving information about the nature of the research and the aim of the current study, participants received either the paper copy of the study or a link to complete the questionnaire online. Fifty-one patients agreed to complete the questionnaire one month later to test the reliability of the measure. The Intolerance of Uncertainty measure, which has been suggested to capture the fear of unknown happening, has been selected to test the construct validity of the fear of relapse measure. For all analyses, the statistical significance level was set to $p < 0.05$.

RESULTS

Statistical Analysis

The frequency and percentage and number of missing responses for each item has been reported. Each item's correlation with the total score and the Cronbach's alpha coefficient has been calculated for all items to study the internal consistency of the measure. Correlation analysis between FoR's score and DASS and IUS was calculated to test the external validity of the scale. The test-retest reliability has been examined using a Spearman Correlation. A Bland-Altman plot (**Figure 1**) was used to display the difference between two times FoR completion and against the average of them. Confirmatory Factor analysis has been hired to examine the internal validity of the scale. To test the external validity and for the convergent validity, the correlation between FoR, DASS, and IUS has been reported. For the discriminant validity, pooled item factor analysis has been performed and the average variance extracted was compared to the square of correlation.

Depression, Anxiety, and Stress

Based on the DASS scores, patients' depression was between 0 and 20 with the mean = 8.30 ± 6.0 which is in normal range.

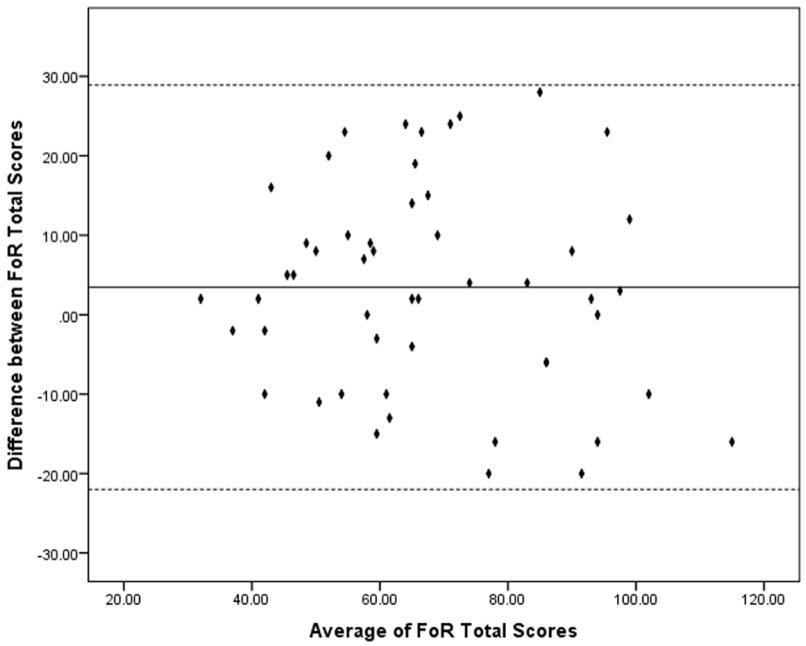

FIGURE 1 | Bland-Altman plot: differences between two times completion of the Fear of Relapse (FoR) Scale by the average of the two scores. Dotted lines indicate the interval that includes 95% of differences between the first and the second assessment.

None of patients had severe depression and was not excluded from analysis. Anxiety was between 0 and 14 with the mean = 6.90 ± 4.4 which is in normal range. None of patients had severe anxiety and was not excluded from analysis. Stress was between 1 and 21 with the mean = 10.86 ± 5.3 which is in normal range. None of patients had severe stress and was not excluded from analysis.

Properties of the Fear of Relapse Scale

Responses to 31 items of the Fear of Relapse Scale are summarized in **Table 1**. Total FoR score were between 0 and 113 (mean = 41.6, SD = 21.1). The total score did not follow a normal distribution and showed skewness to the right. In addition, there was no correlation between the FoR total score and the duration of the disease or the number of relapses or time since their last relapse.

Internal Consistency

Each item was correlated with the total score with a correlation value greater than 0.366 (ps <0.001) (**Table 2**). Cronbach's Alpha was equal to 0.924.

Test-Retest Reliability

Spearman's rank coefficient was selected to measure test-retest reliability for items independently. All items showed a high correlation (Spearman's rank coefficients ranged from 0.349 to 0.815 [ps < 0.05]). A Pearson correlation conducted to measure the test-retest reliability of the total score showed to be significant 0.74 ($p < 0.001$). **Table S1** presents results of the test-retest correlation analysis. **Figure 1** presents the Bland-Altman plot. The difference between two times completion of the FoR is ranged between 28 and −20 (average 3.45 ± 12.98). All the differences fall within 95% confidence of interval from the mean. Regression analysis with the difference score as the dependent variable and the mean of two times completions as the predictor suggest that there is no proportional bias against the mean ($t = -0.927$; $p = 0.36$).

Factor Analysis

A Principal axis factor with Varimax rotation of item from the Fear of Relapse Scale was conducted on the data gathered from patients with RRMS. An examination of the Kaiser-Meyer Olkin measure of sampling adequacy suggested that the sample was factorable (KMO = 0.851; $p < 0.001$).

The results of an orthogonal rotation of the solution are shown in **Table 3**. When rotated factors items with loadings less than 0.45 were excluded, the analysis yielded a three-factor solution (five items have been suggested to be removed: 1, 24, 26, 30, 31). Only one item (#27) was loaded on two components. **Table 3** presents the result of the factor analysis. Cronbach's Alpha after removal of the five items mentioned above went down from 0.924 to 0.917.

Validity

To test conduct validity of the Fear of Relapse Scale we used a Pearson correlation analysis to examine the correlation between the Fear of Relapse Scale (total score after removing five items, three components as the result of factor analysis) and IUS score on two factors and DASS subscales (Depression, Anxiety, Stress). **Table 4** presents the result of the correlation analysis. All the correlations were significant (ps < 0.001).

TABLE 1 | Number of responses for all items of the fear of relapse scale (percentage).

Items	Never	Rarely	Sometimes	Often	Always	Missing
1. I feel another relapse is about to happen whenever I get red eyes or feel pain behind my eyes.	73 (43.5)	42 (25)	28 (16.7)	15 (8.9)	9 (5.4)	1
2. Another relapse means another hospitalization	61 (36.3)	28 (16.7)	41 (24.4)	17 (10.1)	19 (11.3)	2
3. My appearance gives away the fact that I am experiencing a relapse.	68 (40.5)	38 (22.6)	33 (19.6)	16 (9.5)	10 (6)	3
4. Each relapse means the disease is spreading in the nervous system.	34 (20.2)	40 (23.8)	52 (31)	25 (14.9)	13 (7.7)	4
5. I do a lot of exercises because I am afraid of experiencing a relapse.	67 (39.9)	41 (24.4)	28 (16.7)	19 (11.3)	12 (7.1)	1
6. I don't drive in fear of a relapse.	111 (66.1)	11 (6.5)	14 (8.3)	9 (5.4)	21 (12.5)	2
7. Whenever a relapse happens, it can only be managed with more corticosteroids.	57 (33.9)	23 (13.7)	35 (20.8)	26 (15.5)	25 (14.9)	2
8. The disease will come back in the form of a relapse if I stop taking medication for one month.	50 (29.8)	34 (20.2)	32 (19)	17 (10.1)	32 (19)	3
9. Each relapse takes me one step closer to becoming bedridden.	52 (31)	37 (22)	38 (22.6)	24 (14.3)	17 (10.1)	0
10. Each relapse will make me more dependent on other people.	48 (28.6)	33 (19.6)	29 (17.3)	29 (17.3)	28 (16.7)	1
11. Thinking about relapses makes my heart jitter.	42 (25)	35 (20.8)	40 (23.8)	27 (16.1)	23 (13.7)	1
12. After each relapse, I put all my task and duties aside.	60 (35.7)	49 (29.2)	33 (19.6)	16 (9.5)	8 (4.8)	2
13. A severe relapse with strong symptoms can result in death.	115 (68.5)	24 (14.3)	20 (11.9)	6 (3.6)	3 (1.8)	0
14. Any experience of numbness and tingling in my limbs means I am having another relapse.	47 (28)	51 (30.4)	40 (23.8)	17 (10.1)	13 (7.7)	0
15. Heat can trigger a relapse.	26 (15.5)	39(23.2)	39 (23.2)	38 (22.6)	26 (15.5)	0
16. Relapses cause memory decline.	47 (28)	31 (18.5)	44 (26.2)	30 (17.9)	14 (8.3)	2
17. Relapses cause loss of control over movement and posture stability.	32 (19)	36 (21.4)	39 (23.2)	36 (21.4)	24 (14.3)	1
18. When I think about relapse, I am unable to think about anything else.	43 (25.6)	47 (28)	29 (17.3)	21 (12.5)	25 (14.9)	3
19. Grave news can trigger a relapse.	20 (11.9)	33 (19.6)	54 (32.1)	39 (23.2)	20 (11.9)	2
20. Due to fear of a sudden relapse, I try not to take a shower when I am home alone.	143 (85.1)	13 (7.7)	6 (3.6)	3 (1.8)	3 (1.8)	0
21. Relapses worsen the level of fatigue I feel.	25 (14.9)	27 (16.1)	46 (27.4)	38 (22.6)	31 (18.5)	1
22. Relapses can cause urine and stool incontinence.	78 (46.4)	27 (16.1)	33 (19.6)	18 (10.7)	8 (4.8)	4
23. I try not to go out much due to the fear of experiencing a sudden relapse.	118 (70.2)	13 (7.7)	18 (10.7)	11 (6.5)	6 (3.6)	2
24. Thinking about the disease decreases my libido significantly.	83 (49.4)	28 (16.7)	28 (16.7)	13 (7.7)	15 (8.9)	1
25. I don't accept new tasks due to fear of relapses.	97 (57.7)	20 (11.9)	23 (13.7)	18 (10.7)	8 (4.8)	2
26. A bad headache can be a sign of a sudden relapse.	64 (38.1)	51 (30.4)	30 (17.9)	11 (6.5)	9 (5.4)	3
27. Whenever I drop anything, I think I am about to have a relapse.	69 (41.1)	41 (24.4)	27 (16.1)	19 (11.3)	12 (7.1)	0
28. The thought of experiencing a relapse makes me cry.	67 (39.9)	27 (16.1)	22 (13.1)	19 (11.3)	32 (19)	1
29. Not knowing when the next relapse is going to happen is very annoying to me.	83 (49.4)	24 (14.3)	18 (10.7)	17 (10.1)	24 (14.3)	2
30. I think increased sensitivity to exercises or tastes can be a sign of relapse.	129 (76.8)	21 (12.5)	10 (6)	6 (3.6)	2 (1.2)	0
31. Blurred vision or double vision can be a sign of relapse.	16 (9.5)	26 (15.5)	45 (26.8)	41 (24.4)	40 (23.8)	0

A two-component solution factor analysis by pooling the 26 items of the FoR and DASS items (principal components, varimax rotation, maximum iterations for convergence = 50, excluding values below 0.35) resulted in a clear separation of two scales on two components. For the DASS only items 4, 15, and 19 weighted below 0.35, and for the FoR, only item 20 weighted below 0.35. For the DASS items 3, 5, and 15 loaded on both components while the weight on the first component related to other DASS items (respectively 0.615, 0.592, 0.707) was much higher than the weight for on the second component related to FoR items (respectively 0.358, 0.376, 0.353). For the FoR, only the item numbered 16 loaded on both components, while the weight for the second component related to FoR items (0.418) was higher than the weight on the first component (0.415). The average variance extracted for both FoR and DASS (0.702) is higher than the square of correlation between FoR and DASS (0.589). Hence discriminant validity is established.

A similar analysis using the IUS items instead of the DASS resulted in a clear separation of two scales on two components. For this analysis, only the item numbered 20 of the FoR weighted below 0.35 and was removed. Besides, only two IUS items (1 and 7) were loaded on both components. Both items were loaded on the first component (along with other IUS items; respectively 0.438, 0.608) higher than the second component related (along with FoR items; respectively 0.397, 0.393). The average variance extracted for both FoR and IUS (0.637) is higher than the square of correlation between FoR and IUS (0.498). Hence discriminant validity is established.

DISCUSSION

The most common phenotype of MS known as relapsing-remitting MS appears in the form of unpredictable relapses that are associated with the progression of the disease and may result in irreversible damages to the sensations and functions of a person. Like other chronic diseases, fear of consequences, worsening, and relapse is a dominant part of MS as well. The nature of fear and the source of fear have not been investigated very well in the literature on MS. Only a few studies compared the patients' fear of falling between different age groups of MS patients (19). Understanding and the management of fear in chronic diseases have been suggested to be associated with the improvement in self-management in patients (20). Consequently, improved self-management in chronic disease has been suggested to be associated with an improvement in health status, increase in self-efficacy, and a reduction in hospitalization (21). Thus, increased self-management of a chronic disease reduces the economic and emotional burden of the disease and might result in a substantial increase in the quality of life of patients with chronic illnesses (22). Relapses in MS with unknown course and severity are a big source of anxiety in patients and contribute to the development of fear in

TABLE 2 | Internal consistency of the Fear of Relapse Scale.

Item	Item-total correlation	Score (mean ± SD)
1. I feel another relapse is about to happen whenever I get red eyes or feel pain behind my eyes.	.366**	1.07 (1.2)
2. Another relapse means another hospitalization	.541**	1.43 (1.4)
3. My appearance gives away the fact that I am experiencing a relapse.	.521**	1.16 (1.2)
4. Each relapse means the disease is spreading in the nervous system.	.594**	1.65 (1.2)
5. I do a lot of exercises because I am afraid of experiencing a relapse.	.370**	1.21 (1.3)
6. I don't drive in fear of a relapse.	.453**	0.9 (1.5)
7. Whenever a relapse happens, it can only be managed with more corticosteroids.	.564**	1.63 (1.5)
8. The disease will come back in the form of a relapse if I stop taking medication for one month.	.601**	1.68 (1.5)
9. Each relapse takes me one step closer to becoming bedridden.	.622**	1.51 (1.3)
10. Each relapse will make me more dependent on other people.	.575**	1.74 (1.5)
11. Thinking about relapses makes my heart jitter.	.686**	1.72 (1.4)
12. After each relapse, I put all my task and duties aside.	.583**	1.17 (1.2)
13. A severe relapse with strong symptoms can result in death.	.428**	0.56 (1)
14. Any experience of numbness and tingling in my limbs means I am having another relapse.	.513**	1.39 (1.2)
15. Heat can trigger a relapse.	.371**	1.99 (1.3)
16. Relapses cause memory decline.	.548**	1.6 (1.3)
17. Relapses cause loss of control over movement and posture stability.	.664**	1.9 (1.3)
18. When I think about relapse, I am unable to think about anything else.	.742**	1.62 (1.4)
19. Grave news can trigger a relapse.	.635**	2.04 (1.2)
20. Due to fear of a sudden relapse, I try not to take a shower when I am home alone.	.305**	0.27 (0.8)
21. Relapses worsen the level of fatigue I feel.	.623**	2.14 (1.3)
22. Relapses can cause urine and stool incontinence.	.453**	1.09 (1.2)
23. I try not to go out much due to the fear of experiencing a sudden relapse.	.499**	0.64 (1.1)
24. Thinking about the disease decreases my libido significantly.	.497**	1.1 (1.3)
25. I don't accept new tasks due to fear of relapses.	.559**	0.92 (1.3)
26. A bad headache can be a sign of a sudden relapse.	.475**	1.09 (1.2)
27. Whenever I drop anything, I think I am about to have a relapse.	.609**	1.19 (1.3)
28. The thought of experiencing a relapse makes me cry.	.622**	1.53 (1.6)
29. Not knowing when the next relapse is going to happen is very annoying to me.	.650**	1.25 (1.5)
30. I think increased sensitivity to exercises or tastes can be a sign of relapse.	.298**	0.4 (0.8)
31. Blurred vision or double vision can be a sign of relapse.	.460**	2.38 (1.3)

TABLE 3 | Item factor loading for the final solution on 26 final items of the Fear of Relapse Scale.

Item	Component		
	1	2	3
2. Another relapse means another hospitalization	0.75		
9. Each relapse takes me one step closer to becoming bedridden.	0.719		
10. Each relapse will make me more dependent on other people.	0.712		
11. Thinking about relapses makes my heart jitter.	0.694		
7. Whenever a relapse happens, it can only be managed with more corticosteroids.	0.663		
18. When I think about relapse, I am unable to think about anything else.	0.651		
4. Each relapse means the disease is spreading in the nervous system.	0.615		
12. After each relapse, I put all my task and duties aside.	0.564		
28. The thought of experiencing a relapse makes me cry.	0.547		
8. The disease will come back in the form of a relapse if I stop taking medication for one month.	0.543		
29. Not knowing when the next relapse is going to happen is very annoying to me.	0.542		
27. Whenever I drop anything, I think I am about to have a relapse.	0.495	0.495	
3. My appearance gives away the fact that I am experiencing a relapse.	0.488		
16. Relapses cause memory decline.		0.713	
14. Any experience of numbness and tingling in my limbs means I am having another relapse.		0.659	
15. Heat can trigger a relapse.		0.64	
21. Relapses worsen the level of fatigue I feel.		0.629	
17. Relapses cause loss of control over movement and posture stability.		0.562	
19. Grave news can trigger a relapse.		0.544	
22. Relapses can cause urine and stool incontinence.		0.496	
13. A severe relapse with strong symptoms can result in death.		0.486	
23. I try not to go out much due to the fear of experiencing a sudden relapse.			0.714
5. I do a lot of exercises because I am afraid of experiencing a relapse.			0.708
6. I don't drive in fear of a relapse.			0.61
20. Due to fear of a sudden relapse, I try not to take a shower when I am home alone.			0.597
25. I don't accept new tasks due to fear of relapses.			0.531

Five items with loading weights below 0.45 were removed from the table and the final version of the scale.

TABLE 4 | Correlations between Depression, Anxiety, Stress, Scale, Intolerance of Uncertainty Scale, Fear of Relapse Scale and its Subscales.

	DASS_D	DASS_A	DASS_S	IUS_F1	IUS_F2
FoR_total	.600**	.587**	.588**	.513**	.527**
FoR_Comp1	.540**	.497**	.542**	.491**	.495**
FoR_Comp2	.521**	.546**	.520**	.449**	.458**
FoR_Comp3	.400**	.422**	.338**	.316**	.358**

DASS_D, Depression subscale of DASS; DASS_A, Anxiety subscale of DASS; DASS_S, Stress subscale of DASS; IUS_F1, Factor 1 of the Intolerance of Uncertainty Scale; IUS_F2, Factor 2 of the Intolerance of Uncertainty Scale.
$^{**}p < 0.001$.

patients (23). However, as far as we are aware, fear of relapse and its impacts on the quality of life has not been fully addressed, and we need to develop a scale to screen MS patients. Measuring fear of relapse may help the health care system to treat patients in a more personalized approach. As such, the current study aimed to develop a measure that can quantify fear of relapse in patients suffering relapsing-remitting MS and to validate it in a separate sample of participants.

To test the validity of the Fear of Relapse Scale, the patients were asked to complete two other measures assessing their intolerance of uncertainty (fear of unknown) and stress, anxiety, and depression. Both scales and all subscales were significantly and positively correlated with individuals' total fear of relapse score. The Pearson correlation was at medium range suggesting a relationship between the FoR scale, DASS, and IUS measures. Further investigations, however, showed that when two independent two-components factor analyses were run by pooling items of the Fear of Relapse Scale once with the IUS and once with the DASS, items related to each scale were independently loaded on a separate component, which suggest that in spite of a positive and significant correlation, each of the included measures assess independent constructs. This suggests that inclusion of the fear of relapse in research and clinical work with MS patients can capture characteristics in patients that cannot solely be explained by intolerance of uncertainty, depression, anxiety, and stress in patients.

We tested the reliability based on test-retest and internal consistency, Cronbach's Alpha. The Cronbach's alpha for the scale was 0.94, which is above the suggested threshold for the assessment of reliability (24). In line with this analysis, all items in the measure were positively and significantly correlated with the total score of the scale, which indicates the high internal consistency of the Fear of Relapse Scale (25). Furthermore, the test-retest reliability showed a high positive and significant correlation between each item's score in the test and that item's score in the retest. Above that, the total score of test-retest reliability showed a high, positive correlation (>0.7). Similarly, the Bland-Altman analysis and the plot indicated that there is a high level of agreement between two times completion of the scale and there is no trend or proportional bias in differences between two times completion of the scale. It is important to remember that none of the patients experienced a relapse or any major problem related to their disease within the period between two assessments. Putting these results together it can be suggested that the Fear of Relapse Scale is a reliable measure, but further studies with long-term follow-up of patients are required to examine the ability of the scale to capture changes due to the alterations in the condition of the patient.

A principal component analysis of all 31 original items of the Fear of Relapse Scale resulted in the removal of 5 items and the remaining 26 items loaded on three factors. The first factor includes items that refer to the fear of disability following a relapse. Disability is a concern for many patients who receive MS diagnosis. The link between the experience of relapse and the progress of the disease causes patients to see each relapse as another step towards the disability, and this can result in the experience of excessive hypervigilance and fear of relapse. The second factor includes items related to the fear of the psychological and physiological consequences of a relapse. The difference between this component and the previous one is in the understanding of the fact that disability is not the sole outcome of the disease and relapses. A relapse may cause a lot of secondary problems, which can interfere with the life of the patient, and items in the second component target these aspects. Usually, relapses are followed by short-term (or in some cases an irreversible) losses in the function of the sensory and motor systems in the central nervous system. Uncertainty about the prognosis of the sensory and motor losses and the future of patients' functions is another source of stress feeding their fear of relapse. The third factor includes items indicating limitations resulting from fear. After the diagnosis, many patients become hypervigilant to the potential impact of the disease on their abilities and thus, they may start to withdraw from many activities and stop accepting new challenges. This avoidance may contribute to the development of fear and further disability and lowering self-efficacy. Compared to the other two components, this component relates to the meta-cognition of patients about the existence of fear and its influence on their life.

Fear of relapse in MS is a neglected phenomenon in the studies investigating the psychological aspects of the diagnosis and living with MS. Psychological factors play a crucial role in the quality of life in patients with MS especially due to the chronic nature of the disease (26). A better understanding of a chronic disease requires a comprehensive approach to take different components into account, especially when it comes to the quality of life as a multi-dimensional aspect (27). A previous attempt to develop measures related to the quality of life in MS resulted in the PERSEPP scale ("PERception de la Sclérose En Plaques et de ses Poussées") (28). Five dimensions of that scale target social support, relationship difficulties, fatigue, state of mind and associated sleep disorders, and time perspective. However, fear as a factor related to the understanding of the patient's acceptance of has not received in depth attention there.

Understanding the source of fear in MS patients will assist professionals to grasp a more detailed image of their life to provide more specific and effective interventions (29). It can be suggested that interventions for the improvement of the fear of relapse might be more effective if provided at the earlier stages of the development of the disease (30).

However, this study has limitations too. The sample of patients in the current study had varying disease duration. Although we did not find any association between the duration of the disease and fear of relapse scores, previous studies suggested that the impact of psychological factors in the first year following the diagnosis is stronger on the quality of life of the patients (30). Also, RRMS patients vary greatly in earlier clinical presentations in comparison with more chronic progressive phenotype (31). Future studies with a larger number of patients in their first year following the diagnosis may help us to characterize fear of relapse among them and to compare them with patients who have experienced more relapses and have a longer disease duration. Besides, since the concept of fear of relapse has not been well investigated in the literature, future studies on a diverse group of patients will allow us to examine the content validity of the measure in more detail. Also, long-term follow-up of patients and changes in their FoR scores can give us a more comprehensive image beside the test-retest reliability. Furthermore, the original version of the scale was developed in Persian. The English translation needs to be investigated in English speaking populations. As such, the measure should be the subject for future studies in another language considering linguistic and cultural differences.

Taken together, this study presents a scale for the assessment of the fear of relapse in RRMS patients. Our data provides preliminary evidence of validity and reliability for this scale. The Fear of Relapse Scale presented in this study showed good internal consistency and high test-retest reliability. This measure needs to be tested in future studies to contribute to the understanding of the life of the patients suffering RRMS and may assist clinicians in identifying the specific sources of anxiety in patients and helping them to plan their interventions tailored to the clinical needs of the patient.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Department of Psychology at Shahid Beheshti University, Tehran, Iran. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AK was involved in design, data collection, analysis, and writing. NM was involved in data collection and writing. NR was involved in data collection. TS was involved in data collection. MD was involved in design, analysis, and writing.

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SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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Identifying Functional Mechanisms in Psychotherapy: A Scoping Systematic Review

Timothy A. Carey[1]*, *Robert Griffiths*[2,3], *James E. Dixon*[4] and *Sonia Hines*[5]

[1] Institute of Global Health Equity Research, University of Global Health Equity, Kigali, Rwanda, [2] Mental Health Nursing Research Unit, Greater Manchester Mental Health NHS Foundation Trust, Manchester, United Kingdom, [3] Division of Nursing, Midwifery and Social Work, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom, [4] North West Boroughs Healthcare NHS Foundation Trust, Warrington, United Kingdom, [5] Centre for Remote Health, Flinders University, Alice Springs, NT, Australia

The identification of fundamental mechanisms is an important scientific pursuit in many fields of enquiry. With regard to the development of psychological treatments, understanding the mechanisms through which change occurs such that psychological distress resolves, can enable us to develop more effective and efficient interventions. In the field of psychotherapy, mechanisms are often identified either statistically or conceptually. The most powerful and useful mechanisms, however, are functional rather than statistical or conceptual. More specifically, with regard to mechanisms relevant to psychotherapy, it is difficult to identify what any of these mechanisms actually *do* in a mechanistic sense. That is, the mechanics of putative mechanisms are generally unspecified. In order to obtain a rigorous and comprehensive account of the current mechanisms in psychotherapy, as well as to evaluate their usefulness, a systematic scoping review was conducted. The systematic scoping review did not yield any mechanisms that were expressed in functional terms. We argue that, in order for psychotherapy to improve its effectiveness and efficiency, the standard for what is accepted as a useful mechanism needs to be substantially raised. Only functional mechanisms that express plausible actions consistent with known biological processes should be used to inform therapeutic interventions.

Keywords: mechanisms, psychotherapy, functional, statistical, mediators, neuroscience, change processes, effectiveness

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Netherlands

***Correspondence:**
Timothy A. Carey
tcarey@ughe.org

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INTRODUCTION

In the field of psychotherapy, the term "mechanism" refers to an explanation of how psychotherapeutic interventions translate into events that lead to the desired outcome (1). Kazdin defines a mechanism as "the basis for the effect, i.e., the processes or events that are responsible for the change; the reasons why change occurred or how change came about." (1) (p. 3). As we will explain below, for this systematic review we have included a broad search strategy, however, it is perhaps uncontentious to suggest that functional, physical mechanisms such as negative feedback are more robust and, ultimately, more useful for scientific progression than

nonfunctional, conceptual mechanisms such as "fear-of-fear." Despite the existence of a plethora of approaches to psychotherapy—with several hundred distinct psychotherapeutic models or techniques described to date (2) —it is still not clear exactly how or why these approaches produce their effects (3).

The Importance of Understanding Mechanisms

Understanding how and why psychological treatments work is important for a number of reasons. Firstly, although there is evidence that psychotherapy is helpful for many people who report psychological distress, there is considerable variation between individuals in terms of the amount of change experienced as a result of engaging with therapy (4). Part of this variation no doubt reflects the different ways in which change is defined such as by differences in scores on outcomes measures or reduction or increases in identified behaviors. Indeed, for some clients, engaging with psychotherapy actually seems to lead to negative outcomes such as a deterioration in functioning (5). Greater understanding of the mechanisms of change would help to clarify which clients are likely to gain the most benefit from therapy and under which conditions. Secondly, a better understanding of mechanisms would help to close the theory-practice gap that has been identified as an impediment to the implementation of evidence-based psychological treatments (4, 6, 7). More broadly however, there remains a lack of understanding holistically the way in which psychological effects and biological mechanisms relate and emerge from one another (8). Bridging these gaps will be necessary to move the development of psychotherapies further. As important and powerful as our psychological processes are, we cannot escape our biology. Any model or process that is proposed must be consistent with known biological structures and properties. Substantial progress will only be made when models are developed that genuinely articulate bio psycho social functioning (8). Thirdly, at present, we do not understand whether there is a single mechanism through which psychotherapy effects change, or whether there are actually multiple mechanisms involved. This is an important distinction to make in terms of promoting the most effective and efficient methods to assist in the alleviation of psychological distress. If there is one fundamental mechanism of change then efforts need to focus on how to access and harness this mechanism. If, however, there are multiple mechanisms of change, a number of other decisions might be important such as selecting the mechanism to focus on or investigating whether multiple mechanisms need to be activated simultaneously or in a particular sequence. A more sophisticated understanding of mechanisms, therefore, would contribute to the development of psychological therapies that facilitate change in the most efficient and effective way possible.

Research examining the effects of psychotherapy on different populations has often observed that some people in the control groups show greater improvement than people in the treatment group. The design of such trials, however, means that researchers tend not to focus on the fact that some people who received no treatment will improve more than some people who received the active treatment. Aggregating data and emphasizing instead, central tendencies between the groups, masks this result (9). In fact, Blampied argues that, if we are to create a science of individuals, statistics is, fundamentally, the wrong approach, because the direction of inference in statistics is always from the sample to the population (10). This is exactly the opposite direction that is needed if we are to understand how individuals function. We will never discover fundamental properties of individuals by continuing to accumulate and assess aggregate data. Accordingly, Bolles asserts that, wherever possible, one should avoid statistics, "abolish superfluous rituals and routines, and get on with the business of science" (11) (p. 79). Of relevance here is the observation that "the power and precision of the natural sciences arose because of a focus on invariance or the common, fundamental underlying properties of seemingly distinct objects" (12) (p. 128). Increasing the extent to which programs of research build functional models to test fundamental assumptions by comparing data generated by the model with the data being investigated rather than relying almost exclusively on the accumulation of statistical success in the form of p values of a specified magnitude might begin to move the field in the direction that Blampied envisaged (10). This should not be construed as either/or a debate but rather a matter of balance. Inferential and descriptive statistics are extremely useful in identifying areas for further investigation. A thorough understanding of these areas, however, should be sought by the building and testing of functional models.

How Mechanisms Have Been Defined in Other Fields

To illustrate how the practice of psychotherapy might be improved by the development of a robust mechanistic account of the change process, it is worth considering how other fields have approached this issue. In the field of medicine, for example, aspirin is a commonly used analgesic and antiinflammatory compound. The mechanism through which aspirin reduces pain and inflammation is by inhibiting the production of an enzyme called cyclooxygenase that stimulates the formation of prostaglandins, lipid compounds known to cause inflammation. An unintended consequence of taking aspirin, however, is that it prevents the production of prostaglandins which are important for the health of the stomach and kidneys (13). It is important, therefore, to understand aspirin's effects at a biological level in order to gain the maximum benefit from its use. Although our understanding of aspirin's mechanism of action is relatively advanced, it is certainly not the case that mechanisms are fully understood for all prescribed drugs. The danger of progressing to clinical trials without a clear understanding of a drug's mechanism of action, however, can lead to expensive failures in the late stages of testing and place patients at risk of side effects that are hard to predict. For this reason, it is recommended that researchers who are using clinical trials to evaluate complex interventions understand "…how the intervention works: What are the active ingredients and how are they exerting their effect?"

(14) (p. 1-2). We would add that understanding the active ingredients requires a sound understanding of known biological processes.

In fact, many of the early psychotropic drugs were discovered serendipitously with no clear explanation for their purported mechanisms of action (15). This situation allowed researchers to propose arguments that were seriously flawed in their reasoning (16, 17). For example, it was proposed that, because some medication increased people's levels of serotonin with consequent elevations of mood being observed, then depressed mood must be caused by a serotonin deficiency (18). Once the chemical imbalance hypothesis was introduced it became impossible to remove despite their never being any evidence to support it (18, 19). So, by proposing an explanation that was not linked to any established biological processes, damaging effects have occurred such as the disabling of known homeostatic mechanisms in the brain and an increase in the number of neurotransmitter receptors leading to long-term dependency (19). Once again, the importance of understanding and integrating biological with psychological and social processes is demonstrated.

Having a sound understanding of aspirin's mechanism of action, however, means that it is possible to understand both the intended effects and possible side effects of its use. It also means that the drug can be targeted to treat the people who are most likely to benefit from receiving it. A similarly robust explanation of the mechanisms through which psychotherapy leads to the amelioration of psychological distress would guide future research and support the development of more effective and efficient psychotherapeutic practices.

Putative Psychotherapeutic Mechanisms

A large number of candidate mechanisms have been proposed to explain how psychotherapy exerts an effect. The examples we provide here in no way represent an exhaustive list. A recent meta-analysis of mindfulness-based cognitive therapy for depression, for example, supported the view that therapeutic effects were achieved through alterations to mindfulness, rumination, worry, compassion, or meta-awareness (20). A review of mechanisms in cognitive therapy for depression, however, pointed to the role of cognitive mediation – specifically, changes in "depressogenic schema" (21). A study of cognitive behavioral therapy (CBT) of panic disorder concluded that the mechanisms of change were increased self-efficacy and reduced anxiety sensitivity (22). Another study, however, proposed that CBT for panic disorder achieved its effect through a reduction in "fear-of-fear"; in other words, the tendency to respond fearfully to altered bodily sensations associated with anxiety (23). What can we conclude from the fact that the field of putative psychotherapeutic mechanisms is so diverse? One conclusion could be that different psychotherapeutic orientations and techniques have different mechanisms of action. Currently, there are many apparently different therapies with different methodological frameworks. The extent to which these superficial differences reflect differences in fundamental mechanisms of action, however, is far from clear. Another related conclusion could be that psychotherapy achieves its effects through different mechanisms depending on the nature of the disorder being treated or the diagnosis of the person seeking therapy. Also, a problem that plagues the field in the absence of a functional mechanism is being able to separate a mechanism from the *outcome* or effects of the mechanism. For instance, should increase self-efficacy and reduced anxiety be considered mechanisms of change or the *products* of some mechanistic process?

To increase our capacity to explain how psychotherapy works, efforts have been made to draw from the growing field of neuroscience, using data showing correlations between biological systems (e.g. fMRI scans of activated brain regions) with psychological processes (e.g. the self-reported experience of emotion), (for an example see Cozolino, 2010) (24). Causal inferences are then made between the two. Many of those, however, who have attempted to use this method to explain outcomes in psychotherapy have been forced to concede that examining two events sharing a moment in time (i.e. an experience reported by a person and a corresponding image of the brain metabolizing glucose) is insufficient when trying to explain how each phenomena contributes to the formation of the other (25). Hence, Johansson and Høglend have been led to conclude that: "… no definitive mechanisms of change for any type of psychotherapy have been satisfactorily demonstrated" (26) (p. 8). This view is shared by Kazdin, who argues that "After decades of psychotherapy research and thousands of studies, there is no evidence-based explanation of how or why even the most well-studied interventions produce change, that is, the mechanisms through which treatments operate" (3) (p. 148). Despite the current lack of progress in this area we fully endorse and support efforts to integrate biological with psychological and social processes. Perhaps what is needed is a different approach as to *how* this integration is investigated.

Functional and Conceptual Models

One limitation of mechanisms of psychotherapeutic change proposed to date is that they are generally conceptual rather than functional in nature. The similarities and differences between putative mechanisms outlined in conceptual models can be hard to discern because of the inherent imprecision and potential for ambiguity that arises from the fact that these models are described in purely linguistic terms. As we have seen, reduced "anxiety sensitivity" and "fear-of-fear" have both been proposed as the mechanism of change for CBT for panic disorder (22, 23). Superficially, anxiety sensitivity and fear-of-fear might appear to relate to similar processes, even if they are described using different terminology. Because these two mechanisms are described in purely conceptual terms, however, it is hard to know to what extent they are truly distinct versus overlapping. The issue raised previously is also relevant here in that it can be hard to discern whether a reduced fear-of-fear is a mechanism of change or the result of the workings of a change mechanism.

Conversely, putative mechanisms described by functional models have the advantage that they are expressed in precise mathematical terms. The use of functional models means that potential ambiguity about the nature of the phenomena being described is reduced (27). When functional models are compared

with each other, therefore, it is possible to have greater confidence that they are describing either the same or different phenomena. Recognition of the importance of precise, quantitative models to scientific endeavors is far from being a new idea. Guilford suggested that "the progress and maturity of a science are often judged by the extent to which it has succeeded in the use of mathematics" (28) (p. 1). Much earlier still, Thomson, said in a lecture "When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of *science*" (29) (p. 73).

The history of medical and psychological sciences is replete with theories that aimed to explain the etiology and amelioration of psychological distress, which were considered plausible at the time but have since been disproved. For example, Hippocrates deemed human health (or the idea of equilibrium) as the harmonious balance of four vital humors that governed physiology and mood, a mechanistic theory that persisted for hundreds of years right up to the Medieval and Renaissance eras (30). Problems of health were believed to arise when the balance between these essential humors was lost. For example, melancholy was believed to be caused by an overabundance of black bile (of Greek origins—mela, meaning black, and chole, meaning bile) (31). A similar story arises from another Greek influence which suggested that a wandering womb was the source of anxiety in women—later influencing the descriptor of such conditions as hysteria (hysterikos—Greek meaning from the womb) (31). The familiarity of this language to us today testifies to a tendency to accept mechanistic theories based on purely conceptual descriptions before confirmation can be achieved through functional evaluations of the concepts.

It is our assertion that progress in psychotherapy, in terms of improving its effectiveness and efficiency, will be realized by emphasizing functional models and paying less attention to purely conceptual or statistical models or models that do not seem to relate in any way to known brain processes. In order to obtain a rigorous and comprehensive account of the current mechanisms in psychotherapy, as well as to evaluate their usefulness, a systematic scoping review was conducted.

Review Question

What mechanisms used to account for psychological change in psychotherapy are supported by neurological or biological evidence and are expressed in functional terms?

METHODS

We used the Joanna Briggs Institute methods for scoping reviews of evidence to guide the conduct of this review (32). While a protocol was not registered, one was developed by the authors *a priori* to select the methods and criteria for inclusion before the review was begun.

Inclusion Criteria

Population

The population of interest to this review were adults, with no other restrictions on demography. Studies describing their population as children, adolescents, or pediatric were excluded since we were interested in investigating the change process in a fully developed human brain not in one where the change process might be difficult to disentangle from standard developmental processes.

Concept

The concept of interest was the biological function or process underpinning psychotherapeutic change mechanisms. Eligible studies needed to identify both a change mechanism and a related or underlying biological function or process to be included. A change mechanism was defined as "a specific process through which thoughts, feelings, and behaviors, or some combination of these, was altered" and biological functions or processes were defined as "widely accepted brain activity such as synaptic transmission or signal propagation".

Context

The context of interest was the nexus between neurobiological science and adult psychotherapy.

Types of Studies

Any type of quantitative research study or systematic review that was eligible for inclusion provided it reported evidence of plausible biological functions or processes associated with psychotherapeutic mechanisms of change was eligible for inclusion. Studies published after 2000 in English were eligible for inclusion. Our reasoning for beginning our search with publications from the year 2000 was that this would provide us with two decades of research to scrutinize and would also provide us with a decade of research both before and after Kazdin's comments about the state of our knowledge in this area (3).

Exclusion Criteria

Animal studies, pediatric studies, discussion and opinion papers, studies of the mechanisms or functions of psychoactive medications or other drugs, and studies discussing or proposing mechanisms conceptually or statistically were ineligible for inclusion.

Searches

We searched Medline, PsycINFO, EMBASE, and Google Scholar in May 2019 for research studies and systematic reviews meeting the inclusion criteria. The reference lists of retrieved articles were also screened for potentially relevant articles.

Search strategy

We used combinations of keywords and subject headings to construct search strategies appropriate for each of the databases. Initial keywords were psychotherapy or psychotherapeutic, change mechanism or mechanism of change or mechanism and biological or physical or function. Searches were downloaded from the databases into Endnote X9 (Clarivate Analytics, PA).

The titles and abstracts (where available) of search results were initially screened by two authors working independently to assess the congruence of studies to the inclusion criteria and identify papers to be retrieved in full text. Full text articles were then retrieved and screened independently by two authors to determine final inclusion status.

Data Extraction

We planned for one author to extract data from the included studies. Units of extraction were citation details, study design, setting, and population where available, and details of the psychotherapeutic change mechanism with the related functional, neurological, or biological supporting evidence. It was also arranged that a second author would check the extractions against the papers of any included studies.

Data Synthesis

We planned to use graphs and tables to synthesize the findings of all included studies.

RESULTS

Searching identified 497 potentially relevant citations, with six further papers uncovered from reference list checking for a total of 503 papers for initial consideration. Of the potentially relevant citations, 154 were deemed likely to meet the inclusion criteria and retrieved in full text form. After reading the full text, no studies were retained to inform the analysis as none completely met the inclusion criteria. The flow of studies through the review process is illustrated in **Figure 1**.

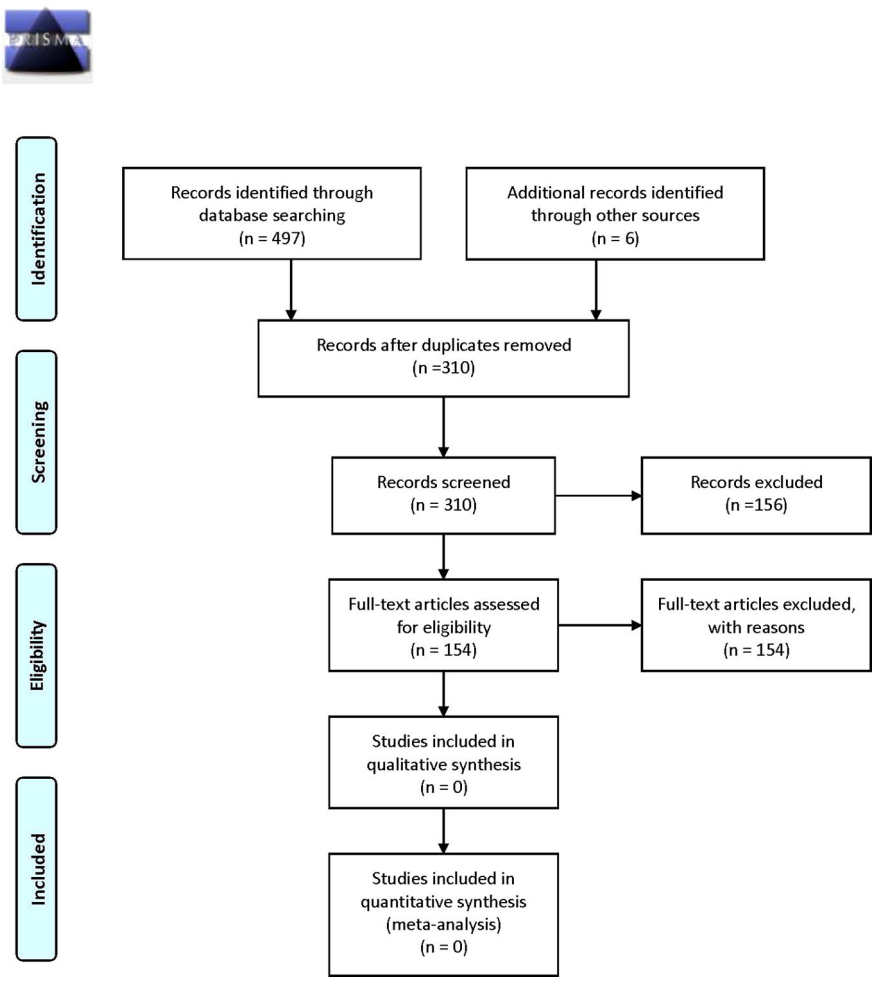

FIGURE 1 | PRISMA 2009 flow diagram.

Of the 154 articles selected for full-text examination, 70 were excluded for not being primary research, 66 for the research not examining functional mechanisms, 10 were systematic reviews, 2 focused on pediatric publications, 2 were not quantitative research, 2 were drug studies, 1 was a study protocol, and 1 article had been withdrawn by the publisher. Reasons for exclusion are further detailed in Appendix A in **Supplementary Material**.

DISCUSSION

In order to more accurately understand the change process in psychotherapeutic treatments, a scoping systematic review was conducted to identify mechanisms that were expressed in functional terms and that had some connection to known neurobiological brain processes. The literature search conducted as part of this scoping review returned numerous putative mechanisms that have been proposed as explanations for how change occurs as a result of engaging with psychotherapy. None of these mechanisms, however, were expressed in functional terms and none were related to known neurological or biological processes. The fact that our search strategy returned no studies for inclusion does not mean that the literature in this field is devoid of useful information. It does mean, however, that there are no current published studies that are able to answer our research question. It also means that a different approach to the consideration and study of mechanisms is further justified.

The majority of mechanisms identified in the process of this scoping review were described in purely conceptual or statistical terms. Whereas functional models aim to describe, in precise mathematical terms, the properties of systems comprising multiple interacting subsystems that are responsible for producing the phenomena of interest, conceptual models have been criticized for their reliance on abstract generalizations (33). The fact that conceptual models are expressed in verbal rather than mathematical terms has also been highlighted as a limitation. Models expressed in purely linguistic terms are inherently ambiguous and susceptible to misinterpretation (27). A consequence of this lack of specificity is that conceptual models are of limited use when trying to describe the inner organization of complex systems that are producing observable behaviour (33).

A proportion of putative mechanisms identified during the review process took the form of descriptions of changes in neural activity in particular areas of the brain (eg. Lueken et al., 2013; Messina, Sambin, Palmieri & Viviani, 2016; Reinhardt, et al., 2010) (34–36). It was not clear, however, how these changes in neural activity constituted a mechanism of change.

The findings of this scoping review are consistent with much of the existing literature on the topic of psychotherapeutic mechanisms, where the lack of plausible mechanisms of change have been identified as a barrier to developing more effective approaches to psychotherapy (1, 3, 26). Indeed, despite the fact that more than a decade has passed since Kazdin published a well cited article outlining this problem, it is disheartening to find that the field of psychotherapy research appears to be no closer to identifying such mechanisms (1).

Although Kazdin's proposed framework for defining mechanisms within psychotherapy using a statistical process has been available for over a decade, not one study was able to meet all the requirements necessary to support a mechanistic conclusion (1). To compound this issue, not one study that we reviewed acknowledged these omissions as a limitation nor held back from making mechanistic inferences.

If we are to acknowledge this fully within the field of psychotherapeutic research, it leads to a possible crossroads in the development in this science. Do we repeat the last ten years and seek to improve the statistical processes used to discover mechanisms or do we do something different? Carey suggested in a review of the way in which psychotherapy creates its effects, that the process of reorganization might be a plausible change mechanism to explain the amelioration of psychological distress generally (37). The model of reorganization suggested by Carey is expressed as a functional model and is consistent with recognized neural processes (33, 37). Furthermore, the reorganization model can account for the nonlinear and unpredictable nature of the change process (38). A model such as this could lead the way to a new and, ultimately, more productive area of research. For progress such as this to occur, however, there needs to be a much stronger link between robust theories and research and clinical practices. That is, both researchers and clinicians working in the psychotherapy field should be required to link their practices to rigorous scientific theories incorporating functional mechanisms and established biological processes.

Kazdin has provided a coherent template for researchers aiming to identify mechanisms of change using statistical methods. This template, however, does not appear to have resulted in increased knowledge about mechanisms (1). It might be the case that were Kazdin's recommendations for mechanistic research implemented rigorously—something that is not happening at present—it might result in the identification of plausible mechanisms (1). Recently, however, there have been calls for changes to evaluation practices to help improve the effectiveness and efficiency of psychological interventions, and to increase progress toward identifying plausible mechanisms of psychotherapeutic change (27, 39, 40). These changes would involve the adoption of a different approach to research practices to the one proposed by Kazdin (1).

Concerns have been expressed about the impact of implicit but frequently unstated assumptions that underpin the research designs of studies in this area (39). One such assumption is that of *linear causality*: the belief that an independent variable (the treatment, intervention, or technique) *causes* changes to the dependent variable (the outcome being measured). This assumption, however, fails to acknowledge that, in the case of psychotherapy, change does not happen independently of the client and therapist. In such circumstances, the treatment does not have any inherent therapeutic properties. Rather, therapeutic change arises from the interaction between therapist and client (41). One consequence of this assumption appears to be that

many researchers have moved to testing psychological interventions, through the use of research designs such as randomized controlled trials (RCTs), without first conducting mechanistic research that could inform the design of such studies. Our position is that substantial progress will be made when research of functional mechanisms is embraced on a much wider scale and incorporated into research programs using designs other than RCTs to explore areas such as the way in which the therapist and the client co-create beneficial outcomes.

Given the current large-scale financial investment in psychotherapy research and practice, the fact that we were unable to identify any mechanisms meeting the criteria of this scoping review is concerning. In the United Kingdom alone, the *Increasing Access to Psychological Therapies* (IAPT) program is estimated to have cost £1 billion to date (42). For ongoing large-scale investment to be justifiable, it is not sufficient for researchers to identify that a relationship exists between attending therapy and improved outcomes. For the field to advance, and for therapists to become more helpful for more people more of the time, it is imperative that we improve our understanding of *how* and *why* engaging with psychological therapy translates into positive outcomes for service users. This will only occur when researchers and clinicians work together in the embrace of scientific theories that have established the role of functional mechanisms through rigorous testing. Only in this way will it be possible to understand which of the many available therapies will be most helpful, under what conditions, and to which people.

Lack of Evidence

The current review of the field, using Kazdin's framework to assess the quality of mechanistic inferences made within psychotherapy research, also highlights further barriers to explaining why and how psychotherapy works (1). It is our position that, even if Kazdin's framework were imposed faithfully, the field is still far short of being able to define mechanisms involved in psychotherapeutic change. A purely statistical approach, we argue, will be insufficient. Looking to achieve the specificity called for by Kazdin, for example, will not be achieved through statistical modeling alone. Statistical models can examine the relationships between concepts, but statistics alone cannot attest to the ecological validity of the concepts being analyzed. In addition, the "meticulous detail" called for by Kazdin, again, cannot be provided through statistical modeling in isolation. Functional examples, working in the real world, are required to genuinely test whether a purported mechanism acts in a mechanistic way.

Again, looking back to history and the evolution of the scientific method suggests the current field researching psychotherapeutic mechanisms is struggling with fundamental epistemological issues. Popper has highlighted that providing incremental information does not necessarily increase knowledge, and warned strongly against using statistical inference alone (43). Further argued by Taleb who highlighted such limitations using the "Black Swan" example attributed to Mill. Hume also called out examples of naive empiricism, showing how induction becomes a problem if applied alongside an incorrect method, such as searching for a mechanism without the correct experimental design (44, 45). Looking for how someone achieves change through a therapeutic process requires the method to capture the adaptation, reorganization, and emergent factors specific to that person. Induction acts against such a focus, minimizing the variance and compressing the detail so as to lose the specific in favor of the general. Aside from these epistemological issues, there appears to be a problem with the applied assumptions and how the problem of mechanisms is being framed. Although we were not able to identify any studies that satisfied the inclusion criteria for this systematic review, we are, nevertheless, able to make the following conclusions:

1. Mechanisms in the psychotherapy field are discussed almost exclusively in conceptual or statistical terms. There is a glaring absence of any sort of progression to more robust, precise, and accurate functional models;
2. Articulation of an integrated, functional bio-psychosocial model is yet to occur with the field still being some distances from understanding how neurological and biological findings can be reliably understood in terms of daily psychological and social functioning; and
3. Years of research, with the aim of discovering the mechanisms of psychotherapeutic change, has not removed the uncertainty around why psychotherapy works for some and not for others. In the 10 years since Kazdin made this observation, we have made little progress addressing this crucial topic (3).

These conclusions can help to consider a problem from the perspective of whether it falls into one of three categories: simple; complicated; or complex (46). Our review would suggest that the problem of identifying therapeutic mechanisms is a complex problem. This is in keeping with conceptualizing psychotherapeutic mechanisms as part of a complex system (33). Complex problems encompass both simple and complicated problems within, but are not reducible to these problems (47). Solving a complex problem requires the solution to account for the special requirements and unique local conditions related to that problem (48), while allowing for parts of the problem to be interdependent (49), and not assuming linear causality (50). Addressing a complex problem requires one to understand that the problem will adapt given a change in conditions (51, 52). The field of research appears to have overlooked such requirements and, hence, has attempted to solve a complex problem using methods and means that are unsuited to the task; a criticism being echoed elsewhere (33, 39). Given Kant's insight that our human powers of observation have built within them natural limitations that are designed to draw us toward inductive, causal interpretations which is an observation that is now further supported by more recent models of brain science and theories of reasoning, it might not be entirely unpredictable that the field of psychotherapy research would have reached the impasse it has (53–55). To find the elusive mechanisms being sought, for increased understanding of psychotherapeutic effectiveness, the field needs to move away

from the ever growing "cobweb of learning" (56), toward functional mechanisms that can be falsified through the use of theory that acknowledges the complexity of the problem and processes related to that problem. Falsification in this sense would entail building simulation models of the proposed mechanisms that are capable of generating data. Then, the data from the model can be compared with the data produced by the suggested mechanism and the degree to which the data match will determine the acceptance or rejection of the mechanism.

CONCLUSION

We argue that, for psychotherapy to improve its effectiveness and efficiency, the standard for what is accepted as a useful mechanism needs to be raised substantially. Only functional mechanisms that express plausible actions consistent with known biological processes should be used to inform therapeutic interventions. The current state of the evidence shows that the science has some distance to progress before we can be certain of the functional mechanisms underpinning psychotherapies.

AUTHOR CONTRIBUTIONS

TC conceived of the concept of the paper and prepared the initial submission as well as the first draft of the paper. SH conducted the searches for the review and led the review of the papers. All authors contributed to the review of the papers. RG and JD contributed substantially to writing and editing drafts of the paper to produce the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00291/full#supplementary-material

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METHODS
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Factorial Designs Help to Understand How Psychological Therapy Works

Edward R. Watkins and Alexandra Newbold*

College of Life and Environmental Sciences, University of Exeter, Exeter, United Kingdom

A large amount of research time and resources are spent trying to develop or improve psychological therapies. However, treatment development is challenging and time-consuming, and the typical research process followed—a series of standard randomized controlled trials—is inefficient and sub-optimal for answering many important clinical research questions. In other areas of health research, recognition of these challenges has led to the development of sophisticated designs tailored to increase research efficiency and answer more targeted research questions about treatment mechanisms or optimal delivery. However, these innovations have largely not permeated into psychological treatment development research. There is a recognition of the need to understand how treatments work and what their active ingredients might be, and a call for the use of innovative trial designs to support such discovery. One approach to unpack the active ingredients and mechanisms of therapy is the factorial design as exemplified in the Multiphase Optimization Strategy (MOST) approach. The MOST design allows identification of the active components of a complex multi-component intervention (such as CBT) using a sophisticated factorial design, allowing the development of more efficient interventions and elucidating their mechanisms of action. The rationale, design, and potential advantages of this approach will be illustrated with reference to the IMPROVE-2 study, which conducts a fractional factorial design to investigate which elements (e.g., thought challenging, activity scheduling, compassion, relaxation, concreteness, functional analysis) within therapist-supported internet-delivered CBT are most effective at reducing symptoms of depression in 767 adults with major depression. By using this innovative approach, we can first begin to work out what components within the overall treatment package are most efficacious on average allowing us to build an overall more streamlined and potent therapy. This approach also has potential to distinguish the role of specific versus non-specific common treatment components within treatment.

Keywords: factorial, mechanism, psychotherapy, specific factors, common factors, cognitive behavioral therapy

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Lorenzo Lorenzo-Luaces, Indiana University, United States

***Correspondence:**
Edward R. Watkins
e.r.watkins@exeter.ac.uk

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INTRODUCTION: THE NEED TO UNDERSTAND HOW PSYCHOLOGICAL THERAPIES WORK

Psychological treatments for mental health disorders have been robustly established as proven and evidence-based interventions through multiple clinical trials and meta-analyses (1–3). Nonetheless, there is a pressing need to further improve psychological interventions: even the best treatments do not work for everyone. Many patients do not have sustained improvement, and treatments need to scaled up to tackle the global burden of mental health (4). For example, psychological treatments for depression only achieve remission rates of 30%–40% and have limited sustained efficacy (at least 50% relapse and recurrence) (1, 5). Further, it is estimated that current treatments, if delivered optimally, would only reduce the burden of depression by one third (6). As such, psychological treatments for depression need to be significantly enhanced.

One pathway to improving the efficacy and effectiveness of therapies is to develop our understanding of how complex psychological interventions work. Despite determining that a number of psychological treatments are effective, for example, cognitive-behavioral therapy (CBT), we still do not know how psychological treatments work. There is little evidence on the precise mechanisms through which psychological treatments work or what are the active ingredients of treatments (7–10), especially for disorders involving general distress such as depression and generalized anxiety disorder. Historically, there has been little progress in specifying the active ingredients of CBT for depression, and as a consequence, there have been no significant gains in the effectiveness of CBT for depression for over 40 years.

Resolving the active mechanisms and active ingredients of psychological interventions has been repeatedly identified as a major priority for research (4, 7, 10, 11). For example, the Institute of Medicine (2015) highlighted the need to identify the key elements of psychosocial interventions that casually drive its effects (11).

To be clear, we distinguish between the active components of therapy, operationalized as the active elements or ingredients within a therapy that produce clinical benefit, which could be therapist-based, client activities, specific techniques, or related to therapy structure and delivery, versus the active mechanisms of the therapy, operationalized as the underlying change processes that causally underpin therapeutic benefit. While active components will necessarily impact on one or more active mechanisms, knowing the most effective components of a therapy is distinct from knowing how this component leads to symptom change [i.e., its underlying mechanism(s)]. For example, in CBT, identifying behavioral activation as an active therapy component does not necessarily confirm that the mechanism-of-action is behavioral as behavioral activation may work through changing cognitions.

Understanding the mechanisms or the active components of psychological treatments are important because either potentially enables the development of more direct, precise, potent, simpler, briefer, and effective treatments. Understanding the active components of a psychological therapy is necessary in order to parse and distil the therapy to focus on what is essential and most engaging to patients.

Psychological treatments are complex interventions, typically made up of multiple elements and components, including the particular content and techniques of the therapy, the interaction between the therapist and patient, the structure of the therapy, and the mode and organization of delivery, each of which potentially acts *via* distinct mechanisms. Therapy is thus a complex multifactorial process. Any or none of these factors could contribute to the efficacy of an intervention, alone or in interaction with the other factors. It is therefore critical to determine the beneficially active, inactive, or inert, and iatrogenic components within an intervention so that the intervention can be honed to become optimally effective, by focusing on the active elements and by removing irrelevant or unhelpful elements (12).

Relatedly, if we know the active mechanisms of an intervention, we may be able to adapt the intervention or develop novel approaches to more directly target this mechanism and, thereby, increase the efficacy of the intervention.

Because of the high prevalence of common mental health problems, there is also a scalability gap because there are not sufficiently available therapists to tackle the global burden of poor mental health (13). It is therefore critical that ways are found to make treatments more efficient, scalable, and easier to train and disseminate. Understanding the underlying components of therapy and being able to remove unnecessary elements may make psychological therapies more effective and more cost-effective by streamlining and simplifying the treatment. For example, the same treatment benefit could be achieved from fewer sessions, enabling a greater volume of patients to be treated for the same volume of therapists. Understanding the critical active components of therapy will also help to adapt treatments for the alternative delivery means that are necessary for increased scalability (for example, to convert for self-help, lay provision, or digital interventions), without losing the core elements needed for efficacy. Understanding how therapy works will also make it easier to effectively train and disseminate therapies, facilitating wider treatment coverage. This understanding may also help to identify moderators of treatment outcome and more effectively personalize therapy to each individual.

COMMON VERSUS SPECIFIC TREATMENT FACTORS

One key issue with respect to resolving the underlying mechanisms underpinning the efficacy of psychological treatments concerns the question of whether treatment works through specific versus non-specific common factors (8, 14). Specific factors are procedures or techniques arising from the particular therapy approach, such as those typically described in structured treatment manuals, for example, cognitive

restructuring in CBT; exposure in CBT for anxiety disorders. Common (or non-specific) factors are those that are hypothesized to be common across all psychological interventions. The most important of these include a positive and genuine relationship between the therapist and patient, engendering positive expectancies and hope in the patient, and a convincing rationale that explains the symptoms experienced and gives credible reasons for the treatment to be helpful (15). There is a long-standing and still unresolved debate between those who propose that psychotherapies mainly work through specific factors versus those who propose that psychotherapies mainly work through common factors.

One argument made in support of common factors is that different specific psychotherapies are generally not found to differ in efficacy, although this does not logically rule out that treatments may work *via* different mechanisms (16). A recent review concludes that there is as yet no conclusive evidence that either common or specific factors can be considered a validated working mechanism for psychotherapy, in other words, the evidence is insufficient to determine the role of either (8).

The relative contribution of common versus specific factors in the efficacy of psychological interventions has important implications for how therapists should be trained, how therapies should be delivered, and for how treatment services should be organized. If the substantive part of the treatment effect is due to common factors, then therapy training should predominantly emphasize therapists learning how to develop a strong therapeutic relationship, develop a rationale etc. In parallel, therapy research should focus on understanding how to strengthen positive common factor effects. However, if specific factors are important then these also need to be emphasized in training and delineated in further research. Furthermore, the increasing importance of specific factors indicates a potentially greater need for discriminating and selecting therapy to match the individual clinical presentation.

METHODOLOGIES TO EXAMINE THE MECHANISMS OF PSYCHOTHERAPY

Comparative Randomized Controlled Trials

One reason for limited progress in understanding the mechanisms of psychological treatments is the focus on parallel group comparative randomized controlled trials (RCTs). Parallel group RCTs are the gold standard for establishing if an intervention works more than another intervention or against a control and the best means for establishing the relative efficacy of one treatment intervention versus another. However, they are not designed for investigating the specific mechanisms of how interventions work or identifying the active components of therapy. Because comparative RCTs can only compare the overall effects of each intervention package, they are not intended to and unable to provide information about the performance of the individual elements within complex multifactorial interventions. In standard comparative RCTs, all of the multiple treatment components and factors in an intervention package and their hypothetical mechanisms are aggregated and confounded together in the comparison of one treatment versus another. As a consequence, this design is unable to test specific main effects of treatment components nor any possible synergistic or antagonistic interactions between individual treatment components, limiting advances in mechanistic understanding. If an RCT finds one treatment better than another, we do not know which components made a difference; if there is no difference, we do not know whether there are any components that effected an improvement.

This limitation of standard comparative RCTs also applies to their ability to resolve the relative contribution of specific versus common factors. One major issue concerns the difficulty in finding an adequate control arm to compare against a putative active treatment to distinguish the role of specific versus non-specific factors. Some comparative RCTs and meta-analyses have found that one therapy has outperformed another therapy (17, 18), which proponents of specific factors have argued as evidence for specific treatment effects. However, proponents of the common factors model have counter-argued that sometimes the comparison treatments used are not bona fide therapies, defined as viable treatments that are based on psychological principles and delivered by trained therapists, and thus that this is not a fair comparison. When comparisons are made between bona fide therapies, no differences in efficacy are found (19).

Relatedly, other designs have compared an active treatment to a psychotherapy placebo or attentional control on the argument that any differential beneficial effect observed for the active treatment will then be due to specific factors as the effects of the attentional control can only be due to common factors. However, most psychotherapy placebos do not control for all the potential common factors hypothesized in therapy, and thus, any difference found between a placebo and an active treatment could be due to either specific or common factors or some combination thereof (20). For example, it is hard to generate psychotherapy placebos that are exactly matched to active treatments in therapy rationale and credibility, without the placebo itself becoming a bona fide treatment. Similarly, psychotherapy placebos tend to differ from active treatments with respect to the structure of the therapy, for example, the number and duration of sessions, training of therapist, format of therapy, and range of topics covered. A meta-analysis of comparative trials found that there were larger effect sizes found between active treatments and structurally inequivalent placebos than between active treatments and structurally equivalent placebos, for which there were negligible differences (20). These difficulties in finding matched placebo controls or bona fide interventions have limited the conclusions that can be reached about the relative contribution of specific or common factors examined in parallel RCTs.

Attempts have also been made in RCTs to determine mechanisms by examining changes in putative mediators. For example, in trials of CBT, measures of change in negative

thinking are examined as a mediator of symptom change. However, these mediational approaches are necessarily limited because they are still indirect and correlational (7). Even if an intervening variable is found to statistically account for the relationship between the treatment and its outcome, this does not provide strong evidence of a mechanism of change, because it does not support a strong causal inference that the mediator influences outcome. In such associations, the mediator may be a proxy to another variable(s) and there may be another unknown or unmeasured variable that is related to both the outcome and the mediator. Ultimately, direct experimental manipulation of the relevant factor is required for strong causal inference, and this is not possible for multiple elements of psychological interventions within a parallel group comparison RCT.

Component Study Designs

One experimental approach that has been used to examine the specific elements of psychological interventions is the component study (9), in which the full intervention is compared with the intervention with at least one component removed (a dismantling study) or in which a component is added to an existing intervention to test whether it improves outcomes (an additive study) (21). In principle, this approach can enable a strong causal inference that a component has a direct effect on outcome if there is a significant difference in outcomes between the variant of the therapy with a component and the variant without that component.

Nonetheless, there are limitations of component designs. First and critically, the component design does not necessarily test the main effect of a component, that is, the difference between the mean response in the presence of a particular component and the mean response in the absence of the particular component collapsing over the levels of all remaining factors. This can be illustrated with reference to one of the seminal dismantling studies—the dismantling study of CBT for depression by Jacobson and colleagues (22). In this study, patients with depression were randomized to either the full CBT treatment package including behavioral activation, cognitive restructuring to modify negative automatic thoughts, and work on core schema, or to behavioral activation plus cognitive restructuring or to just behavioral activation element alone, with 50 patients in each arm. No significant difference was found between the three versions, leading some observers to suggest that behavioral activation alone is sufficient for the effects of CBT on depression. However, it is important to realize that all versions of the treatment involved behavioral activation: as a consequence, for example, the trial is testing the effect of cognitive restructuring in the context of behavioral activation versus behavioral activation alone. It can only tell us the effect of that component in the context of the other component. Thus, the effects estimated are only the simple effects of each component with the remaining component set to one specific level. For example, for cognitive restructuring, this design only reveals the effect of cognitive restructuring in the presence of behavioral activation. It does not test the main effect of cognitive restructuring, i.e., does the presence of cognitive restructuring have a treatment effect relative to the absence of cognitive restructuring. Similarly, because there is no condition without behavioral activation, it is not possible to estimate the direct main effect of behavioral activation.

Second, the component design assumes that there is no interaction between the components, that is, that the effect of one component is independent of the presence or absence of other components. This may not always be a realistic assumption. For example, it is possible that behavioral activation and cognitive restructuring either complement each other or are antagonistic to each other.

Third, there is a concern that most component studies are not sufficiently powered to detect a difference between two potentially active treatment arms. For example, it has been estimated based on the assumption that a minimally clinically important difference for depression is d=0.24 that a trial would need 274 participants in each condition.

The Factorial Approach

We propose the use of factorial and fractional factorial designs as an alternative methodological approach to standard comparative RCTs and component designs, which has advantages over both for resolving the active components of psychotherapy. Factorial experiments allow one to explore main effects of factors and interactions among factors (23–27).

Factorial designs systematically experimentally manipulate multiple components or factors of interest. Indeed, factorial designs are commonly used to test the role of different factors simultaneously in experimental psychology. As such, they meet the requirement for delineating active components raised by multiple commentators (8, 10, 14). For example, the Institute of Medicine (2015, p3-10) recently proposed that "determination of which elements are critical depends on testing of the presence or absence of individual elements in rigorous study designs," which is exactly what a factorial design delivers.

To give a clinical example, if the Jacobson and colleagues dismantling study of CBT for depression was redesigned as a full factorial study, patients would be randomized across three factors [presence or absence of behavioral activation (BA^+ vs BA^-); presence or absence of cognitive restructuring (CR^+ vs CR^-); presence or absence of work on core schema (CS^+ vs CS^-)]. This means that patients would be randomized to be balanced across 8 treatments cells reflecting all of the possible combinations: all three elements (BA^+: CR^+:CS^+); 2 of the 3 elements (BA^+: CR^+:CS^-; BA^+: CR^-:CS^+; BA^-: CR^+:CS^+); 1 of the 3 elements (BA^+: CR^-:CS^-; BA^-: CR^+:CS^-; BA^-: CR^-:CS^+); or none of these elements (BA^-:CR^-:CS^-). This design can test the main effect of each factor as well as their interactions by comparing the mean effects of combined sets of cells against each other. For example, comparing all 4 cells with BA versus all 4 cells without BA tests the main effect of behavioral activation. The difference from the dismantling design is clear because the dismantling design only has 3 of these 8 combinations (BA^+: CR^-: CS^-; BA^+: CR^+:CS^-; BA^+: CR^+:CS^+), which limits it to only testing simple effects.

Factorial designs have been used extensively in engineering to optimize processes. In the last decade, they have been used to good effect in behavioral health, for example, in enhancing interventions for HIV care and prevention (28) and smoking

cessation (29, 30). This approach seems well-suited to expanding to the further understanding of psychological treatments and has been recently adopted in several recent trials (31, 32). We believe that factorial designs have advantages for investigating how psychotherapy works that overcome many of the disadvantages noted earlier for comparative RCTs and component trials, as we will outline throughout this paper.

A fractional factorial design is a variation on the factorial design that employs a systematic approach to reduce the number of experimental conditions to allow a more manageable study, at the cost of allowing only main effects and a pre-specified set of interactions to be tested. Fractional factorial designs require the assumption that higher-order interactions are negligible in size, because they are confounded, or aliased, with lower-order effects.

The IMPROVE-2 Study as an Example of a Factorial Design

We illustrate the use of a fractional factorial design to identify the active ingredients and mechanisms of an intervention, with respect to a specific example - the IMPROVE-2 study (Implementing Multifactorial Psychotherapy Research in Online Virtual Environments) [see (32) for further detail). The IMPROVE-2 study is a Phase III randomized, single-blind balanced fractional factorial trial based in England and conducted on the internet. Adults with depression (operationalized as Patient Health Questionnaire-9 scores ≥ 10) recruited directly from the internet and from an UK National Health Service Improving Access to Psychological Therapies service were randomized across seven experimental factors, each reflecting the presence versus absence of specific treatment components within internet-delivered CBT, guided by an online therapist (activity scheduling, functional analysis, thought challenging, relaxation, concreteness training, absorption, self-compassion training) using a 32 condition balanced fractional factorial design (2_{iv}^{7-2}) (see **Table 1**).

All components involved brief prescribed therapist online support to improve retention and adherence, in which secure online written feedback was provided at the end of each completed module (typically fortnightly), with the option for additional secure messaging between therapist and patient. Therapist feedback highlighted positive steps made, encouraged participants to continue to practice previously introduced components, addressed questions and homework, and pointed out areas to focus on in the next module. Therapists

TABLE 1 | Experimental groups of the IMPROVE-2 fractional factorial design.

Condition	Functional analysis	Concrete training	Compassion	Absorption	Relaxation	Activity scheduling	Thought challenging
1	no	no	no	no	no	yes	yes
2	yes	no	no	no	no	no	no
3	no	no	yes	no	no	no	no
4	yes	no	yes	no	no	yes	yes
5	no	no	no	yes	no	yes	no
6	yes	no	no	yes	no	no	yes
7	no	no	yes	yes	no	no	yes
8	yes	no	yes	yes	no	yes	no
9	no	yes	no	no	no	no	no
10	yes	yes	no	no	no	yes	yes
11	No	yes	yes	no	no	yes	yes
12	yes	yes	yes	no	no	no	no
13	no	yes	no	yes	no	no	yes
14	yes	yes	no	yes	no	yes	no
15	no	yes	yes	yes	no	yes	no
16	yes	yes	yes	yes	no	no	yes
17	no	no	no	no	yes	no	yes
18	yes	no	no	no	yes	yes	no
19	no	no	yes	no	yes	yes	no
20	yes	no	yes	no	yes	no	yes
21	no	no	no	yes	yes	no	no
22	yes	no	no	yes	yes	yes	yes
23	no	no	yes	yes	yes	yes	yes
24	yes	no	yes	yes	yes	no	no
25	no	yes	no	no	yes	yes	no
26	yes	yes	no	no	yes	no	yes
27	no	yes	yes	no	yes	no	yes
28	yes	yes	yes	no	yes	yes	no
29	no	yes	no	yes	yes	yes	yes
30	yes	yes	no	yes	yes	no	no
31	no	yes	yes	yes	yes	no	no
32	yes	yes	yes	yes	yes	yes	yes

*Every factor occurs an equal number of times at high and low levels (i.e. balanced) and all factors are orthogonal to each other. Each effect estimate involves all 32 of the conditions in **Table 1**, thereby maintaining the power associated with all participants. This Resolution IV design means that all main effects are aliased with 3-way and higher interactions, and all 2-way interactions are aliased with 2-way and higher interactions, on assumption that non-negligible 3-way interactions are unlikely. In contrast, a standard RCT is aliased for all main effects and interactions of treatment components.*

were low-intensity Psychological Wellbeing Practitioners and an experienced clinical psychologist.

The IMPROVE-2 trial used a fractional factorial design to retain the benefits of a factorial design while making the study more logistically manageable and feasible to deliver: this fractional factorial design reduces the total number of conditions from 128 to 32. Each component has two "levels" to be compared in the fractional factorial design: either present or absent, i.e., the respective treatment modules are either provided or not provided in the internet platform. IMPROVE-2 therefore tests the main effects and selected interactions for these 7 components within internet CBT for depression to determine the active ingredients of internet CBT. We first outline the general framework used for this study—the Multiphase Optimization Strategy (MOST)—and then explore the particular benefits and methodological issues of using the factorial design to study psychotherapy.

THE MULTIPHASE OPTIMIZATION STRATEGY (MOST)

Within IMPROVE-2, the factorial design is used as one stage within a wider framework for improving interventions—the Multiphase Optimization Strategy (MOST) (33–38) approach. MOST, rooted in engineering, agriculture, and behavioral science, is a principled and comprehensive framework for optimizing and evaluating behavioral interventions (33–38).

MOST consists of three stages: a preparation stage in which the relevant factors and components to be investigated are identified; an optimization stage in which a factorial experiment is used to evaluate the main effects and interactions of each factors; and then an evaluation stage, in which an optimized intervention based on the results of the previous trial is tested in a RCT. MOST has been established to enhance treatments for smoking cessation, with earlier factorial designs identifying active components (29), which were then combined into a novel intervention which outperformed recommended standard care in a RCT (39). MOST is well-validated (29, 30, 34, 40) and recommended within the Medical Research Council Complex Intervention guidelines (41, 42). A key advantage is greater experimental efficiency, with a focus on identifying "active ingredients" versus "inactive" or extraneous components before moving onto large-scale comparative trials, resulting in fewer overall resources required to answer the research questions in the long run than with the traditional approach (43). However, to date, MOST has not been applied to psychological interventions for mental health.

The IMPROVE-2 trial is one of the first attempts to apply the MOST approach to psychological interventions, building on the preparation and optimization phases so far. It incorporates the MOST approach with an internet delivery format for CBT to build in treatment reach, scalability, and increased treatment coverage for the optimized treatment from the start, as the goal is to develop an optimized and scalable evidence-based treatment. Another benefit of using such an internet-delivered therapy is that treatment content can be standardized and fixed, and written therapist responses can be closely demarcated, reducing unwanted "drift" from treatment protocols. This helps prevent potential contamination between different treatment components, which is an important consideration for a factorial design.

The Preparation Stage in MOST

During the preparation stage, a conceptual model for the intervention is developed, and discrete and distinct intervention components are selected. These components are then pilot tested for acceptability, feasibility, evidence of effectiveness, and ease of implementation, and refined as needed. MOST also involves the identification of the optimization criterion, which is the operational definition of the target change sought that is used to judge the optimal intervention, subject to resource or other constraints. For example, this might be greatest symptom improvement that could be obtained for a particular cost or for a particular duration of treatment.

With respect to the IMPROVE-2 study, a previous feasibility study (IMPROVE-1) established that it was feasible to maintain treatment integrity and fidelity across randomization into multiple treatment conditions and to avoid contamination across treatment conditions. Because the IMPROVE-2 study is focused on determining the ingredients of internet-CBT that are most effective for treating major depression in adults, the operational definition for the optimization criterion was the largest reduction in depressive symptoms, as indexed by using change in scores on the Patient Health Questionnaire-9 score (PHQ-9) (44) as the primary outcome.

Components Within the Psychological Intervention

A key step within this preparation phase is to identify the components that are to be targeted. When planning a factorial study, the best components to choose are those that are: related to a specific conceptual model; distinct from each other in content, approach or delivery method; have some evidence of efficacy, that can be independently administered, i.e., one component is not dependent on another for delivery; and that are hypothesized to address one or two theoretical mediators. In essence, it is important that components can be distinguished from each other in a meaningful way and that they are conceptually related to different mechanisms.

The elements or components selected can be at different levels of analysis and abstraction. The level selected will depend on the specific question or conceptual model. For example, for CBT, the components chosen could relate to the main hypothesized theoretical mechanisms of change and their associated elements, such as activity monitoring and scheduling and detecting and testing automatic thoughts. Alternatively, the components could relate to lower-level, more discrete elements within the treatment techniques such as the behavioral change techniques outlined in a recent taxonomy (45). These behavioral change techniques include behaviors such as self-monitoring,

goal-setting, and feedback, which are common across different CBT components as well as other psychotherapy modalities. Alternatively, the components could relate to process-related aspects of therapy such as whether the intervention is therapist-supported versus unsupported, or structural aspects, such as the frequency of treatment sessions.

IMPROVE-2 illustrates the selection of components to be examined. Consistent with the principles above, the IMPROVE-2 study chose treatment components that were conceptually and operationally distinct from each other, so that each can be evaluated independently. As the first attempt to disentangle the active components within CBT for depression, components were chosen that were clearly distinct and that could be linked to the main theorized mechanisms of action in CBT. These components were operationalized at a relatively high-level (e.g., thought challenging to reflect cognitive theories of change; activity scheduling to reflect behavioral theories of change) rather than in terms of the more localized behavioral change taxonomy because the goal was to determine the core components relating to key theoretical conceptualizations of CBT and to maximize the likelihood of finding a positive effect. If, for example, thought challenging was found to be a strong active ingredient, then further studies could dissect which elements including more specific behavioral change techniques are critical to the effects of thought challenging. Three of the components chosen had been identified as elements for CBT for depression, using a Delphi technique (46): applied relaxation; activity monitoring and scheduling; detecting and reality testing automatic thoughts. A further component—functional analysis—is a mainstay of behavioral approaches to depression including behavioral activation (47). Three components related to recent treatment innovations in CBT derived from experimental research (48, 49), with each hypothesized to specifically target distinct mechanisms arising from different theoretical models: self-compassion, concreteness training, and absorption. The components selected relate to three theoretical accounts of how CBT might work: a behavioral account, a cognitive account, and a self-regulation account.

Three components related to behavioral models of depression and of how CBT works. Depression has been hypothesized to result from a reduction in response-contingent positive reinforcement (50), in which the individual with depression experiences less reward and sense of agency as a consequence of changing circumstances (e.g., loss), poor skills, or avoidance and withdrawal. Within the behavioral conceptualization, *activity scheduling* is hypothesized to increase response-contingent positive reinforcement by increasing frequency of positive reinforcement thorough building up positive activities. This treatment component provides psychoeducation about the negative effects of avoidance, includes questionnaires to help patients identify their own patterns of avoidance, provides guidance on activity scheduling to build up positive activities and reduce avoidance (e.g., breaking plans into smaller steps; specifying when and where to implement activities), and exercises in which participants generate their own activity plans.

In parallel, *functional analysis* seeks to determine the functions and contexts under which desired and unwanted behaviors do and don't occur and, thereby, find ways to systematically increase or reduce these behaviors, by exploring their antecedents, consequences, and variability, and then either alter the environment to remove antecedent stimuli that trigger unwanted behaviors and/or practice incompatible and constructive alternative responses to these antecedents. This approach is based on Behavioral Activation (BA) (51) and rumination-focused CBT (49) approaches to depression. More specifically, functional analysis is proposed to target habitual avoidance and rumination by identifying antecedent cues, controlling exposure to these cues, and practicing alternative responses to them (52).

Absorption training is also hypothesized to increase response-contingent positive reinforcement by increasing direct contact with positive reinforcers. Absorption training is focused on teaching an individual to mentally engage and become immersed in what he or she is doing in the present moment to improve direct connection with the experience and enhance contact with positive reinforcers. It is designed to overcome the effects of detachment and rumination which can prevent an individual experiencing the benefits of doing positive activities. When delivered within the internet treatment, patients complete a behavioral experiment using audio-recorded exercises to compare visualizations of memories of being absorbed versus not being absorbed in a task, practice generating a more absorbed mind-set using downloadable audio exercises, and identify absorbing activities.

Two components within the factorial design are based on a cognitive conceptualization of depression, in which the negative thinking characteristic of depression, is hypothesized to play a causal role in the onset and maintenance of depression, and, thereby, reducing negative thinking is hypothesized to be an active mechanism in treating depression (53, 54). Central within CBT for depression is the use of thought challenging or cognitive restructuring to reduce negative thinking (55), and this forms one component in the IMPROVE-2 trial. The internet treatment module that delivers the thought challenging component involves psychoeducation about negative automatic thoughts and cognitive distortions, vignettes of identifying and challenging negative thoughts, and written exercises in which patients practice identifying and then challenging negative thoughts using thought records.

The other cognitive-based component involves concreteness training, based on an intervention found to reduce symptoms of depression in a previous RCT (48) and derived from experimental research indicating the benefits of shifting into a concrete processing style (56, 57). Within the IMPROVE-2 trial, the internet treatment module that delivers this component involves psycho-education about depression, rumination, and overgeneralization, a behavioral experiment using audio-recorded exercises to compare abstract versus concrete processing styles, and downloadable audio exercises to practice thinking about negative events in a concrete way. Unlike thought challenging, concreteness training does not test the accuracy or veridicality of negative thoughts but rather trains patients to focus on the specific and distinctive details, context, sequence

("How did it happen?"), and sensory features of upsetting events to reduce overgeneralization and improve problem-solving. *Concreteness training* is therefore hypothesized to specifically reduce the overgeneralization cognitive bias identified as important in depression (53, 58).

The remaining treatment components are hypothesized to directly improve emotional regulation. *Relaxation* is hypothesized to improve self-regulation by targeting physiological arousal and tension. In IMPROVE-2, a variant of progressive muscle relaxation and breathing exercises was used to reduce physiological arousal and tension in response to warning signs, based on trial evidence that this intervention alone reduces depression (48). The treatment component introduces a rationale for relaxation, provides an online relaxation exercise as a behavioral experiment to test if it reduces tension, and a downloadable relaxation exercise.

Self-compassion training is proposed to activate the soothing and safeness emotional system, hypothesized to be downregulated in depression (59). Recent research has highlighted the potential benefit of increasing self-compassion in treatments for depression (49, 60–62), although self-compassion has not yet been directly tested within a full-scale clinical trial for patients with major depression. Within this treatment component, patients read psychoeducation about compassion including useful self-statements to encourage and support oneself, complete a behavioral experiment that compares their own self-talk to how they talk to others, try an audio-recorded exercise visualizing past experiences of self-compassion to activate this mind-set and test its benefits, which is downloadable for further practice, and identify activities they would do more of and activities they would do less of to be kinder to themselves.

The Optimization Stage of MOST: Factorial Experiments and Their Benefits

The second stage of MOST involves optimization of the intervention, typically through a component selection experiment (sometimes called a component screening experiment), using a factorial or fractional factorial design. This factorial experiment is used to specifically determine the individual effects of each component and any interactions between components. It is important to note that this step could involve multiple experiments and an iterative process of further refining the intervention. For example, if the first component screening experiment observed statistically significant moderators of treatment outcome, such as mode of treatment delivery or location of treatment, a further experiment could be conducted in which the moderators are introduced as factors into the factorial experiment so that they are directly manipulated to enable stronger causal inference about their potential contribution to outcome.

Advantages of Factorial Design

There are at least four advantages to the use of a factorial design in resolving how therapy works and what its active mechanisms are.

Advantage 1: Directly Testing Individual Components and Their Interactions

The factorial experiment provides direct evidence about the effects and interactions of individual components within a treatment package, which is necessary for methodically enhancing and simplifying complex interventions (41). It can test each individual component and determine its main effect. Critically, it can also determine possible interactions between components, which other experimental designs are unable to do. Thus, a factorial design has distinct advantages when one needs to determine whether the presence of one component enhances or reduces the effect of another. This approach enables us to identify the active components of therapy and to select active and reject inactive/counter-productive components or elements. By comparing the presence versus absence of each component, this factorial design can examine the main effect of each component on the primary outcome, for example, testing whether thought challenging reduces symptoms of depression.

With respect to the IMPROVE-2 study, it is important to note that despite the many trials of CBT for depression, no trials have directly tested the main effect of each of the selected treatment components—for example, does thought challenging have a direct effect on reducing depression relative to no thought challenging? This design therefore provides the first fully-powered test of the main effects of these ingredients of CBT for depression. **Table 1** describes the specific combinations of the two-level intervention factors in the experimental design.

To illustrate how the factorial design works, consider **Table 1**. Main effects and interactions are estimated based on aggregates across experimental conditions. For each main effect, half of the study population are randomized to one level of the factor (e.g., in conditions 9–16, 25–32, presence of concreteness training) and half will be randomized to the other level of the factor (e.g., in conditions 1–8, 17–24, absence of concreteness training). Therefore, the main effect of concreteness training can be determined by comparing the average effect of conditions 9–16, 25–32 versus conditions 1–8, 17–24.

Technically, the IMPROVE-2 study is an internet-delivered component selection experiment with seven experimental factors evaluated, each at two levels ((presence, coded as +1 versus absence, coded as -1 of component, effect coded), using a 32-condition balanced fractional factorial design (2_{IV}^{7-2}). Effect coding is used because it ensures that main effects and interactions are independent.

A full factorial design of seven factors would have required $2^7 = 128$ conditions, which was deemed to be impractical and too complex to program and administer, and thus a fractional factorial design was chosen. For IMPROVE-2, a 2^{7-2} fractional factorial design was chosen, which reduces the number of experimental conditions by a factor of four, down to 32 conditions. While the full factorial design necessarily includes all possible combinations of all factors, within a fractional factorial design the researcher has to strategically and carefully select a subset of the experimental conditions available.

The first consideration when selecting the subset of the experimental conditions is statistical, with a need to maintain a

balanced design in which every factor occurs at an equal number of times at each of the two levels, and in which all factors are orthogonal to each other. This necessarily limits the potential configurations of subsets available. These designs can be mapped out using factorial design tables (63) or statistical packages (e.g., PROC FACTEX in SAS).

The second key consideration is to select the subset of experimental conditions that maximizes the ability to estimate the main effects and interactions that are of highest priority for the research question. Typically, estimating the main effects of the intervention components is a priority. For a fractional factorial design, some of the main effects are going to be confounded (typically referred to as "aliased" within the factorial literature) with higher-order interactions, and thus the subset of experimental conditions needs to be carefully selected so that the main effects are only aliased with higher-order interactions that are judged to be less likely to be significant (e.g., 3-way or 4 way-interactions) or of less theoretical interest.

For IMPROVE-2, the selected design allows the estimation of all main effects and several pre-specified 2-factor interactions among the seven intervention factors; in statistical terminology, it is a Resolution IV design because main effects are only aliased with 3-way and higher interactions. This means that if a potential effect is observed for a particular component, technically the observed effect is due to the sum of the main effect itself and the specific aliased higher-order interactions, i.e., the estimated lower-order effect may include contribution from these higher-order effects. For example, the main effect of concreteness is aliased with the 4-way interaction of functional analysis by compassion by absorption by thought challenging, and the 4-way interaction of functional analysis by compassion by relaxation by activity scheduling and the 5-way interaction of absorption by concreteness by relaxation by thought challenging by activity scheduling. Thus, the actual effect observed is due to the sum of the main effect plus the 4-way and 5-way interactions. If this comparison is significant, the most likely explanation is that the presence of concreteness training produces better treatment outcomes than the absence of concreteness training although we cannot rule out in the fractional design that configurations of 4 and 5 components, albeit unlikely, could contribute to this effect. In interpreting the results, the assumption is that the 3-way and higher interactions are highly likely to be negligible, based on extensive research and principles within factorial experiment research (27, 63). Although in most cases this assumption is reasonable, it may not always apply.

In designing the study, several 2-way interactions were pre-specified as being of particular interest, where it was hypothesized that components might interact with each other, and the design was explicitly chosen so that these 2-way interactions were only aliased with 3-way or 4-way interactions, which we typically expect to be negligible. For example, it was hypothesized that activity scheduling and absorption treatment components may have a positive synergistic effect because the former increases the number of positive activities engaged in, whereas the latter increases the potential absorption and connection with these activities. Similarly, it was hypothesized that thought challenging and self-compassion components may have a positive synergistic effect because thought challenging helps individuals to look logically for evidence against and alternatives to negative self-critical thoughts, while self-compassion encourages a more kindly and tolerant approach to tackle self-criticism.

One choice within the design of the fractional factorial is whether or not it includes the experimental condition in which all intervention components are set to the low level or absent, i.e., a no-treatment control. For the purposes of investigating the active ingredients of therapy, this condition is not necessarily required, since the logic of the factorial experiment is not to compare all the conditions directly with each other, as we would in a comparative RCT, but rather to identify the active components by aggregating mean effects across each factor.

For IMPROVE-2, the fractional factorial design explicitly excluded the condition in which participants receive no treatment components. This has several potential advantages. First, it means that there is not a no-treatment or treatment-as-usual condition, so that the design and trial was suitable for use in a clinical service, where it would not be possible or ethical to randomize patients to not receive any active treatment. Second, because all participants are randomized to active treatment, they are more likely to remain engaged in the trial and to not judge that they are receiving the "inferior option" as can sometimes occur for control conditions.

Within the IMPROVE-2 fractional factorial design, all participants were randomized to receive at least one component of CBT and in the majority of cases 3 or 4 components of CBT. Based on the experience of the IMPROVE-1 feasibility study, in which many patients only completed their first few treatment modules, the IMPROVE-2 counter-balanced the order in which the treatment modules delivering each treatment component were received in the internet platform to ensure that each component was received equally often across all participants as patients progressed through the therapy. In this way, the number and order of treatment components was equivalent between the high (presence) and low levels (absence) of each factor. Of course, this leaves open the question of whether the order of receiving treatment components might be important or not: given the iterative nature of the MOST approach, the effect of sequencing treatment components on efficacy could be a further question for a subsequent component screening experiment.

Advantage 2: Manipulation of Hypothesized Mechanisms and Examination of Individual Mediators

The factorial design allows research on the working mechanisms and mediators that allows strong causal inference because each factor associated with a hypothesized specific mechanism is manipulated and the effect of manipulating this factor can be tested directly on secondary measures indexing the putative mediator. The design also enables examination of the mediators of each individual intervention component, because each factor is manipulated independently. For example, this design can test whether the presence of a thought challenging

component has a main effect on reducing self-reported negative thinking relative to the absence of thought challenging, and whether this change in thinking mediates change in depression.

To maximize this opportunity to test mediators, the IMPROVE-2 trial required all patients to complete a series of self-report questionnaires at baseline and at each follow-up assessment (at 12 weeks and 6 months post-randomization), as well as after each completed treatment module that index all the putative mediators across all the treatment components. For each treatment component, the putative mediator was related to the primary mechanism which each treatment component is hypothesized to most strongly influence, including rumination (5-item Brooding scale) (64) for the functional analysis component, overgeneralization (adapted Attitudes to Self Scale – Revised) (58) for the concreteness component, self-compassion scale (65) for the self-compassion component, negative thinking (Automatic Thoughts Questionnaire) (66) for the thought challenging component; increased behavioral activity and reduced avoidance (Behavioral Activation for Depression Scale Short-form) for the activity scheduling component (67), and absorption and engagement in positive activities, adapted from measures of "flow" for the absorption component (68). Mediational analyses can then be used to test the hypotheses that each treatment component primarily works through the hypothesized mediator, using the analytical approach outlined by Kraemer et al. (69) and modern causal inference methods. In addition, IMPROVE-2 will investigate potential moderation of the treatment components by site, age, sex, severity of depression, co-morbid illness, and antidepressant use. This design enables us to test whether manipulating a particular component influences the underlying process it is hypothesized to change, and whether that process in fact mediates symptom change. By assessing all putative mediators for all components, we can also test whether components influence other processes, e.g., whether components tackling behavior change cognition or vice versa.

Advantage 3: Improved Delineation of Specific Versus Common Treatment Factors

The factorial design provides a stronger test of the relative contribution of specific versus non-specific common treatment factors than existing designs. As noted earlier, the majority of control comparisons are inadequate for disentangling specific from non-specific treatment effects because of the difficulty in creating psychotherapy placebos (attentional controls) that match a bona fide psychotherapy for credibility, rationale, and structure. However, the factorial design overcomes this limitation because for any treatment component (e.g., the relaxation component in IMPROVE-2), the aggregate of the conditions where it is present (i.e., **Table 1**, conditions 17–32) are equivalent for treatment credibility, structure, delivery, rationale, therapist contact, therapist content and techniques and therapist allegiance with the aggregate of the 16 conditions where it is absent (i.e., **Table 1**, conditions 1–16), except for the specific treatment component itself. Moreover, these conditions are also matched in aggregate for all the other six treatment components, since these are balanced in the design. The evaluation of the main effect of relaxation involves the comparison of the average effect for the conditions where relaxation is present versus for the conditions where relaxation is absent. This design therefore provides the strongest control condition available and one that is able to disentangle specific from non-specific common treatment factors. More specifically, this approach is a rigorous test of whether there are specific treatment effects arising from particular treatment components in addition to any non-specific factors common across the treatment components. If there is a significant main effect for any component in IMPROVE-2, then this is strong evidence for a specific treatment effect above and beyond all the non-specific common therapy factors present in CBT. The nature of the non-specific factors tested will depend on the specific components compared in the trial design: because IMPROVE-2 exclusively examines components within internet-CBT, it confounds non-specific factors common across therapies (e.g., therapeutic alliance, rationale) and those specific to internet-CBT and common to all components (e.g., self-monitoring; homework). A different study that took components from different treatment interventions could better delineate non-specific effects common to all therapies. This approach would not rule out some contribution of common factors to treatment outcome, as common factors would be matched across the two levels of the factor, but would be definitive evidence for a specific treatment effect. Conversely, if none of the components were found to have a significant main effect (assuming sufficient power), this would suggest that any treatment benefit was due to common factors.

Advantage 4: Factorial Designs Are Efficient and Economical

Factorial designs are efficient and economical compared to alternative designs such as individual experiments and single factor designs because they often require substantially fewer trials and participants to achieve the same statistical power for component effects, producing significant savings in recruitment, time, effort and resources (23, 43).

For example, as an alternative to the factorial design used in IMPROVE-2, a research program could investigate each of the components separately in seven individual experiments or conduct a comparative RCT or a component trial (dismantling or additive design). For IMPROVE-2, it was assumed that the smallest Meaningful Clinical Important Difference (MCID) would be a small effect size (Cohen's d or standardized mean difference=.2) for the main effect of an individual treatment component or interaction between components on pre-to-post change in depression. An alpha of 0.1 was chosen as this is recommended for component selection experiments to decrease the relative risk of Type II to Type I error when selecting treatment components; i.e., to avoid prematurely ruling out potentially active treatment components (23, 36). In order to detect a MCID of d = 0.20 with 80% power at $\alpha = 0.10$ per treatment, a sample size of N=632 was required (NQuery 7.0). Because participants provide at least five repeated measures on the primary outcome, latent growth curve modeling can be used, which was conservatively estimated to reduce sample size by 30% relative to only using first and last time-point as in an Analysis of

Covariance, but then numbers were increased to account for estimated 40% dropout attrition post-treatment, giving a required total sample of N= 736 for the fractional factorial design.

However, the same MCID, power and attrition issues apply for all other trial designs. Thus, each individual experiment would need 736 participants to be adequately powered to examine each component: conducting seven separate experiments to investigate each of the seven components would require N= 5,152, or seven times as many participants as the factorial experiment. A parallel comparative RCT to compare each of the components against each other and against a no-treatment control would have 8 arms and require 368 participants per arm, thus requiring N=2,944, or four times as many participants as the factorial experiment. Similar calculations apply for component experiments – for example a dismantling study that compares a full treatment package (all seven treatment components combined), with incrementally dismantled packages, each with a component removed (i.e., all components minus compassion; all components minus compassion and absorption, etc.) would have 7 arms (assuming there is not a no-treatment control), each requiring 368 participants per arm, requiring N=2,576, or 3.5 times as many participants as the factorial design.

Factorial and fractional factorial designs are efficient and economical because rather than making direct comparisons between experimental conditions as in the other designs, the factorial design compares means based on aggregate combinations of experimental conditions. To illustrate within IMPROVE-2, as indicated in **Table 1**, the estimate of the main effect of concreteness training is based on comparing the aggregate of conditions 9–16, 25–32 where it is present, versus aggregate of conditions 1–8, 17–24 where it is absent; the estimate of the main effect of relaxation is based on comparing sum of conditions 1-16 versus sum of conditions 17–32; the estimate of the main effect of thought challenging is based on comparing sum of conditions 1, 4, 6, 7, 10, 11, 13, 16, 17, 20, 22, 23, 26, 27, 29, 32 versus the sum of conditions 2, 3,5,8, 9, 12, 14, 15, 18, 19, 21, 24, 25, 28, 30, 31, etc. In this way all participants are involved in every effect estimate—it effectively recycles each participant by placing each participant in one of the levels of every factor. As such, the full sample size can be used to determine each of the main effects, making this design efficient for power and sample size.

The Evaluation Stage of MOST

The third stage in MOST is the evaluation of the optimized intervention. An optimized intervention is systematically built from the results of the factorial experiment by including the most active components with strongest effect sizes relative to the pre-specified optimization criterion, but excluding and eliminating weak inert or antagonistic components. This optimized intervention is tested against the standard evidence-based treatment in a parallel comparative RCT. Thus, to be clear, the MOST approach still retains the parallel comparative RCT as the best method to evaluate one treatment package against another, but adds the factorial design as the most efficient means to investigate the treatment components. In this way, the MOST framework uses rigorous design to identify active elements of a treatment, build a potentially better therapy and then test whether it is an improvement on existing active treatments.

IMPROVE-2 has not yet reached the optimized intervention and evaluation stage. Nonetheless, the logic is clear: based on the results of the IMPROVE-2 factorial experiment, a refined internet CBT treatment package would be produced by retaining those treatment components that had the largest effect sizes for depression, and by removing those components that had minimal or even negative effect sizes. Both the Pareto principle and prior MOST studies suggest that there will be variability in the treatment effect sizes of different components and their interactions, that not all components will be active in the therapeutic benefit of CBT, and indeed, that many will have insignificant effect sizes (30). As such, it should be possible to concentrate the therapy elements to make CBT more potent, and as a minimum more effective.

This process also considers any potential interactions between components. For example, if there was a significant positive two-way interaction between two components, such that adding one component to the another produced larger treatment effects than either on their own, then these factors may be added to the treatment package. In contrast, if there was a significant negative antagonistic interaction between two components, such that together the treatment benefit was less than either on their own, the component with the weakest positive main effect would be probably removed from the treatment package.

If an examination of the estimated effect size of the optimized intervention from the component selection experiment looked favorable, then this optimized intervention would then be tested against an established internet CBT for depression treatment package, to test whether these modifications improved treatment outcome. If the optimized intervention looked unlikely to outperform existing treatments in the modeling of the treatment estimates, or was found to not be superior in a subsequent comparative RCT, then the MOST logic is that further iterations through the three phases are needed. If this approach indicates that some but not all components within internet CBT for depression have a significant effect size in reducing depression, it will lead to the building of better therapies that focus on the active ingredients and discard inert or iatrogenic elements.

POTENTIAL LIMITATIONS

The IMPROVE-2 trial is only one illustration of how the factorial approach could be used to delineate the active components of psychological therapies. As is true for any single study, it has specific limitations. First, it is relatively complex in utilizing seven components. This has the advantage of testing multiple putative active ingredients at once but the risk that with this complex design main treatment effects may be diluted. Adequate testing of treatment components in the factorial design requires each component to be delivered with sufficient difference between the presence and absence of the component to provide a fair test of its main effect. Because the components in IMPROVE-2 each reflect exposure to specific treatment content and techniques, this means that participants need to

receive a sufficient dose of the respective content and techniques, that is, complete the relevant modules and practice the relevant behaviors. We sought to achieve this by having each component as a distinct module that is completed over several weeks, and whose content and techniques are then referenced and checked and practised in all subsequent modules and explicitly referred to in the subsequent written feedback from the therapist, to maintain their ongoing use. This meant that the "dose" of treatment elements should be comparable to proven internet CBT treatments and sufficient for testing the main effects.

Nonetheless, there are alternative approaches to tackling this issue. One alternative way to increase treatment dose would be to have a simpler design with fewer treatment components that each run over multiple modules. Another alternative is to test process-focused components such as the degree or nature of therapist support (e.g., support versus no support), or structural components such as the frequency of treatment sessions (e.g., weekly or twice weekly), both of which involving keeping therapy content constant. Such designs straightforwardly deliver a sufficient difference between the presence and absence of the treatment component. Of course, the selection of different components necessarily tests different hypotheses as to the active ingredients of therapy. At this point, it remains an empirical question which of these different components most contributes to treatment outcome. Each approach is equally valid. This is why we strongly advocate for multiple factorial trials to test these different dimensions so that we can systematically enhance therapy.

Related to this limitation, IMPROVE-2 used a fractional factorial design, which raises the potential risk of main effects being confounded with higher-order effects. While this risk is deemed to be very low because 3-way and 4-way interactions are unlikely to be significant, a full factorial design would avoid this assumption. A full factorial would be more suitable for designs utilising fewer components.

A further limitation of the IMPROVE-2 design is that all the components utilize a CBT framework and include generic CBT elements such as self-monitoring, planning, homework and homework review, Socratic review, building new activities, collaboration with the therapist, and a common CBT rationale focusing on thoughts and behavior. As such, if we were to find no main effects for any of the treatment components, we could not determine to what extent any treatment benefit observed was due to non-specific effects common across therapies (such as therapist alliance, remoralization) or due to non-specific effects particular to CBT. Nonetheless, this design still provides a better matched control to investigate specific main effects than prior designs and to test if there any specific main effects. Either pattern of findings (identifying one or more specific main effects of treatment components versus no main effects observed) would still be an advance on our current knowledge and could then be further explored further within the MOST framework.

DISCUSSION

We have reviewed the importance of better understanding the mechanisms and active ingredients of psychological treatments in order to refine, condense, and strengthen the potency and effectiveness of these treatments. We have shown that standard comparative RCTs and component trials have limitations for determining the specific treatment contributions of individual treatment components within a psychological treatment package and for inferring causality concerning treatment mechanisms. We have shown how factorial and fractional factorial trials can overcome these limitations and have the particular advantages of directly testing individual components and their interactions, of examination of individual mediators and experimental manipulation of hypothesized mechanisms, of being able to distinguish specific factors from common treatment factors, and of being economical and efficient with respect to sample size and resources.

This approach has been illustrated with respect to the IMPROVE-2 trial (32), which will provide the first examination of the underlying active treatment components within internet CBT for depression. Understanding the active components of therapy will enhance our understanding of therapeutic mechanisms and potentially enable the systematic building of more effective interventions. The IMPROVE-2 trial has completed the recruitment, treatment and follow-up stages, with 767 adult patients with depression recruited, and statistical analyses underway. It is anticipated that these analyses will significantly extend our understanding of how CBT works. We believe that this innovative approach may provide a useful means to address recent requests for rigorous study designs to determine which elements within psychological interventions are core active components (4, 7, 10, 11).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The study protocol for IMPROVE-2 was reviewed and approved by the South West National Research Ethics Committee, NHS National Research Ethics Committee SW Frenchay (reference number, 14/SW/1091, 30/4/2015). The trial sponsor is the University of Exeter, contact person Gail Seymour, Research Manager.

AUTHOR CONTRIBUTIONS

EW and AN both designed, prepared, and delivered the IMPROVE-2 study. EW prepared the first draft of the manuscript, AN commented on the draft, and both EW and AN finalized the manuscript.

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REVIEW
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Why Do We Need Computational Models of Psychological Change and Recovery, and How Should They Be Designed and Tested?

Warren Mansell[1]* *and Vyv Huddy*[2]

[1] School of Health Sciences, University of Manchester, Manchester, United Kingdom, [2] Clinical Psychology Unit, University of Sheffield, Sheffield, United Kingdom

Traditional research methodologies typically assume that humans operate on the basis of an "open loop" stimulus-process-response rather than the "closed loop" control of internal state. They also average behavioral data across repeated measures rather than assess it continuously, and they draw inferences about the working of an individual from statistical group effects. As such, we propose that they are limited in their capacity to accurately identify and test for the mechanisms of change within psychological therapies. As a solution, we explain the advantages of using a closed loop functional architecture, based on an extended homeostatic model of the brain, to construct working computational models of individual clients that can be tested against real-world data. Specifically, we describe tests of a perceptual control theory (PCT) account of psychological change that combines the components of negative feedback control, hierarchies, conflict, reorganization, and awareness into a working model of psychological function, and dysfunction. In brief, psychopathology is proposed to be the loss of control experienced due to chronic, unresolved conflict between important personal goals. The mechanism of change across disorders and different psychological therapies is proposed to be the capacity for the therapist to help the client shift and sustain their awareness on the higher level goals that are driving goal conflict, for sufficiently long enough to permit a trial-and-error learning process, known as reorganization, to "stumble" upon a solution that regains control. We report on data from studies that have modeled these components both separately and in combination, and we describe the parallels with human data, such as the pattern of early gains and sudden gains within psychological therapy. We conclude with a description of our current research program that involves the following stages: (1) construct a model of the conflicting goals that are held by people with specific phobias; (2) optimize a model for each individual using their dynamic movement data from a virtual reality exposure task (VRET); (3) construct and optimize a learning parameter (reorganization) within each model using a subsequent VRET; (3) validate the model of each individual against a third VRET. The application of this methodology to robotics, attachment dynamics in childhood, and neuroimaging is discussed.

Keywords: functional model, psychotherapy, mechanism of change, Perceptual Control Theory (PCT), dynamic models

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Veena Kumari,
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United Kingdom

Reviewed by:
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Nottingham Trent University,
United Kingdom
Lola Cañamero,
University of Hertfordshire,
United Kingdom

***Correspondence:**
Warren Mansell
warren.mansell@manchester.ac.uk

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INTRODUCTION

It is well recognized that randomized controlled trials, in isolation, cannot identify the mechanism of action of a psychological therapy (1–3). Most commonly, tests of mechanism involve prospective studies or experimental designs (3, 4). In an earlier review, we identified a number of fundamental limitations with using these methods in psychology, despite their almost universal acceptance (5). In the current article, we will begin by explaining how these limitations specifically apply to research on the mechanisms of psychological therapy. We then propose an alternative method that addresses these issues—building and testing computational models against real-world data. Arguably, this is the ultimate test of a theory —that it specifies a working model that has identical properties to the real system. We will share a number of methodologies and initial findings of this work, utilizing an integrative psychological framework known as PCT (6–9).

WHAT ARE THE LIMITATIONS OF EXISTING METHODOLOGIES WITHIN PSYCHOLOGICAL THERAPIES?

A case has been made regarding the limitations of randomized controlled trials of therapies in being able to understand how a given psychological intervention has its effects (1–4). Psychological interventions are typically complex, multifaceted treatments, and so in a typical controlled trial, it is not clear which of the various active components of the treatment could account for any differences. The situation can be improved by tweaking a certain element of the intervention and comparing the different versions of the intervention experimentally (3, 4). However, there is little evidence that this approach has yielded insights into more effective treatments (10). The element of trial and error in this process means progress is likely to be slow and expensive if a significant proportion of experimental trials do not yield improvements.

While this research provides a window on potential mechanisms of change, these studies are based on a number of assumptions regarding the nature of human behavior and scientific research that challenge the interpretation of their findings (5, 11, 12). These issues can be summarized in four points. First, there is a lack of appreciation within current research design that behavior continuously feeds back on sensory input (such as when you move your head and eyes to continuously change what you are perceiving within your surroundings). Second, there is a lack of theories that acknowledge the continuous and dynamic variation in behavior at the level of the individual, leading to methods that artificially choose to "chunk" or average measurements of behavior instead. Third, there is a disjunct between making an inference about an internal mechanisms of change in psychological therapies within an individual, and the use of group statistics to research the efficacy of psychological therapies on the "average" of a group of individuals, or to assesses statistical trends in a variable (e.g., individual differences in a putative mechanism of change) across a group of individuals. Mediation analyses attempt to determine what variables are pertinent to change. For example, mindfulness may have an effect on outcome *via* rumination and worry (13). However, this approach examines group statistics to understand individuals. An established line of research on the relationship between self-efficacy on performance has found this can lead to opposite relationships at the level of group averages and individuals. Individual differences in self-efficacy demonstrate a positive association with performance compared to analyzing change in self-efficacy within individuals—where the opposite relationship is shown to occur (14). Thus, studies of this kind show that it is possible for group statistics to generate erroneous conclusions regarding the processes occurring within the individual.

Fourth, most theories of psychopathology and the mechanisms of psychological therapies are described verbally. Even if they are operationalized through a diagram, this is rarely in a form that could form a working model that would be necessary to test it against real-world data (15).

The traditional approach to psychological therapy research contrasts with progress of the physical sciences and engineering, and to some extent biology. They have utilized functional model building (16). For example, the theory of aerodynamics is used within computer simulations to model the flight ability of a new aircraft prior to manufacturing. The accuracy of these models is extremely high, which is required in order to assure their feasibility, safety and economic performance. With the fast pace of development of both virtual reality and robotic systems, there is now the potential for models of behavior and cognition to be tested with similar precision (5).

HOW CAN COMPUTATIONAL MODELING PROVIDE ROBUST TESTS OF PSYCHOLOGICAL THEORIES OF THERAPY?

The computational modeling approach requires the mathematical specification of a theory. The challenge this poses is how a theory of psychological change can be described in mathematical terms. In a key article on this topic, Moutoussis and colleagues (17) argue that since psychological therapy requires learning, this allows the computational understanding of learning to be applied to psychological change in therapy. They go on to highlight how learning and inference is central to how Cognitive Behavioral Therapy (CBT) has been conceived from its development onward. One example that Moutousssis and colleagues expand on in their paper is the mapping of inferential distortions to problematic beliefs (17). They provide an example of how a computational model of avoidance learning can be applied to understanding exposure and response prevention. This model specifies key inferences about the outcomes of behavior as the main variables in the models and can be compared to actual behavior. We will return to the modeling of learning later in the article.

There is also a body of earlier work that has focused on the modeling of appraisal and affect that could be applied to

psychotherapeutic change (18, 19). Some of these appraisal models have extended their reach to artificially intelligent systems and complex robotic devices (20). There are also computational models of individuals that model the dynamic relationship between constructs used in cognitive case conceptualizations such as catastrophic thoughts, avoidance, arousal, and cognitive restructuring (21, 22).

Returning to the suitability of computational modeling of beliefs, there is indeed considerable evidence that negative, catastrophic or self-critical beliefs are associated with self-reported distress (23). However, there are also reasons to suggest that personal goals (values, principles, standards, and ideals) may be more fundamental. For example, there is evidence that the content of intrusive experiences such as memories (24) and auditory hallucinations (25) are closely associated with personally valued goals, and that the degree of distress associated with auditory hallucinations (26), and phobic avoidance (27) is associated with how much they interfere with people's more important, self-definitional goals. As will be described below, another way of conceiving psychological change is to consider it as loss and restoration of control. We will introduce and explain perceptual control theory (PCT) because it provides a definition of control that specifies biologically feasible, mathematical models of control that can be applied to the complexities of the mechanism of psychological therapy.

PCT is derived from control engineering (28), which in turn had its basis within the homeostatic systems of the body (29). According to PCT, control is the achievement and maintenance of a variable at a preselected state through actions that counteract disturbances to that variable (9). This is carried out through circular feedback process between the individual and their environment. The current perception of an aspect of the self or environment (e.g., noise level) is compared to the *reference value* for this variable (e.g., a quiet level). The discrepancy between the two (the *error*), is amplified (by a *gain* factor) and drives actions (e.g., to leave the room) that counteract disturbances (e.g., other people talking loudly) to try to keep the variable at its desired level. PCT proposes that we hold our reference values for a whole range of perceptions of ourselves and the world, and that all our actions are aimed at keeping these close to their preferred level—their "just right" states. People are not necessarily conscious of this process; indeed Powers (9) proposed that people are only aware of a small number of perceptual variables that they are controlling at any one time. It is also important to note that reference values are not necessarily fixed, but can be altered internally as necessary when circumstances change; we will discuss this mechanism when we introduce hierarchies later on. Sometimes, people are unable to keep perceived aspects of the environment in a desired state because they do not have the resources (known as the feedback function in PCT) to do so. These kinds of changes in the environment are termed insuperable disturbances. These factors would be beyond the individual's control and experienced as distressing. For example, it would not be possible to bring back to life a deceased family member, or for a neglected infant to find more capable caregivers.

Figure 1 shows in more detail the components of a single control unit. This is the basic building block of the theory. The diagram clarifies a number of features. Importantly, it shows the boundary between the organism and the environment, with a clear indication that the reference value (r) is situated inside the individual. It is set by the output of another control unit that is situated on the level above; in other words the individual can set and modify their own goals. Within a control unit, an input function (Ki) transforms a physical variable in the environment (Qi) into a perceptual input (p). It is this perceptual signal that is controlled. First, it is subtracted from the reference value to generate an error (e). This is amplified by an output function (Ko) to transform it into an output quantity (Qo) that acts in the environment. It acts *via* the feedback function in the environment (Kf) that counteracts the disturbances in the environment (D) to affect the input quantity such that p is kept as close to r as possible.

PCT utilizes the Test for the Controlled Variable [TCV; (9)]. Mansell and Huddy (5) summarize this approach as follows:

> "…the experimenter aims to set up a design in which the perceptual variables that the participant controls can be inferred by the effect of their actions the controlled variable which is observed by the experimenter … the experimenter needs to (a) characterize the continuous array of perceptual information that is available to the participant through their senses (b) identify or provide the means through which the participant has to control their perceptual input within the environment, and (c) identify or manipulate the disturbances to this control." (p. 310, 5).

These models have been applied across wide domains of psychology. For example, they have been designed to closely emulate tracking a cursor on a computer screen (30), movement across a baseball pitch to catch a flyball (31), and selection of work schedules for nurses (32). In each case, this evidence is consistent with a PCT explanation of human behavior. An important contemporary advance on these models is that they can be used to reliably distinguish between individuals; a "control profile" of each individual can be extracted, at least within the domain of simple motor control (33). However, regardless of whether these conclusions can be critiqued, there remains the question of how models of this kind can be applied to the complexities of change through psychological therapies.

THE CORE PRINCIPLES OF PCT INVOLVED IN PSYCHOLOGICAL DISTRESS AND PSYCHOLOGICAL CHANGE

A series of articles have begun to make the case that a PCT explanation of psychological change is supported by existing computational models (2, 34, 35). These accounts rely on three additional principles within PCT that help to model how psychological change occurs in therapy. These are *hierarchies*, *conflict*, and *reorganization*.

The existence of hierarchies is possibly the simplest to explain, because the concept of a hierarchy within the brain

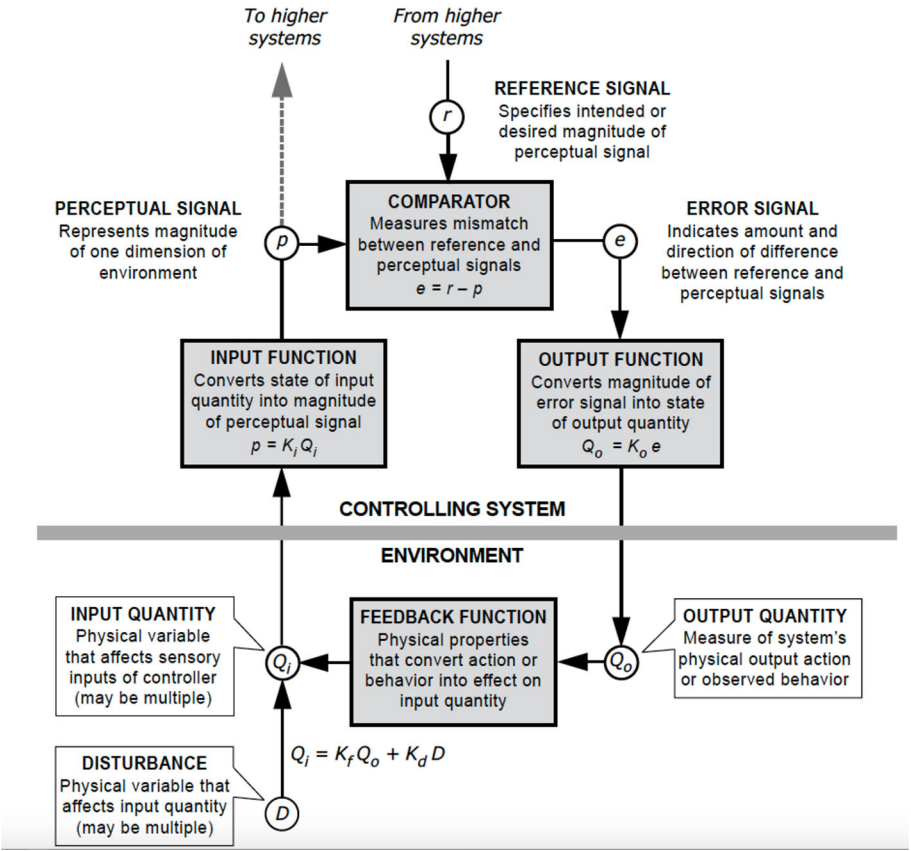

FIGURE 1 | Diagram of the control unit according to perceptual control theory. Permission granted from Dag Forssell, redrawn from an original figure by William T. Powers.

and behavior is common across psychology and neuroscience (36). It is also core to most theories of goals in psychology (37). Hierarchies of control provide a way to organize the many variables that a person strives to control in their life. It also allows flexibility in terms of providing multiple means (lower levels goals) to an end (higher level goal). Thus, Powers et al. (7, 8) proposed that control systems are organized in a cascading, branching hierarchy with the more abstract, fundamental variables (e.g., self-worth and honesty) toward the top, and the more concrete, malleable variables toward the bottom (e.g., perception of proximity to another person, perception of motion). By the 1990s, he had specified eleven levels of this hierarchy through detailed introspection, and each level potentially corresponds to specific fields of psychological inquiry (e.g., sequencing, if-then programming, abstraction of principles). The hierarchy is an essential component to understand how the principles of conflict and reorganization are applied to understand, and model, psychological change.

According to PCT, the psychological distress that entails that a person seeks therapy is a manifestation of loss of control (6–8). It is not, for example, the existence or conviction level of a specific belief, or nature of the inferences that a person makes. The loss of control maybe acute and extreme as in a panic attack, insidious, and biological as in anorexia nervosa, morally threatening such as in obsessions and compulsions, or profound and existential such as in a psychotic breakdown. There are a number of fundamental variables that any human needs to control, and distress is experienced when these are in *error*—when they deviate from their *goal state* or *reference value*. For example, chronic physiological arousal would deviate from the desired state of calmness. An important subset of these fundamental variables are (unlearned) *intrinsic variables*—those maintained by biological control processes in the brain and body—such as body temperature, blood glucose, sleep-activity states, and freedom from pain. Some of these variables will be shared in common with other people, but each individual will inevitably have a different range of controlled variables with differing priorities. The loss of control maybe acute and extreme as in a panic attack, insidious, and biological as in anorexia nervosa, morally threatening such as in obsessions and compulsions, or profound and existential such as in a psychotic breakdown. Indeed, it may possible to map different symptoms of mental health disorders onto specific levels of the perceptual hierarchy. For example, within depression, worthlessness would be experienced at a highest level—the system concept; guilt would be experienced at the principle level; and inability to plan and engage in everyday routines would be experienced at the program level.

People will also differ in terms of the degree of interference, or *conflict*, between the variables they strive to control. For example, in a study of hearing voices in clinical and non-clinical participants, it was the interference between voice hearing and an individual's personal and uniquely specified goals that corresponded with their distress about voice hearing, over and above various properties of the voices (26). Indeed the diagnostic label given to a person's mental health problem may be in a large part explained by the personally important realm of their life in which they have lost control (12).

Following the above account, there are two ways in which psychological distress can be alleviated: by directly enhancing control, and by resolving conflict (35). One successful example of a way to enhance control is to provide patients with the opportunity to determine the timing, appointment scheduling, session length, and duration of their psychological therapy (38). Further successful examples include providing people with the control of the topic of each therapy session (39), or providing them with technology to exert moment-by-moment control of their level of exposure during therapy (40).

Despite the success of addressing control problems directly, helping patients in this way will not be sufficient to address problems of conflict. According to PCT, the majority of cases of chronic loss of control, and therefore long-lasting psychological distress, can be traced to issues of conflict, whether between, or within, individuals (9, 34). Conflict occurs when people attempt to control two or more opposing standards for the same variable. In the case of a specific phobia, for example, the patient may both want to get closer to what they are afraid of in order to overcome their fears and be a strong person, but at the same time want to get further away in order to stop a catastrophic event such as being harmed or humiliated (6). Yet, the experience that the person is trying to control can be completely internal, such as the vividness of memories. On the one hand, a traumatized individual may want to forget their trauma to try to remain sane and get on with their life, but on the other hand they may want to remember their trauma in detail to be a credible witness in court and get justice.

It is notable that Powers' (9) theory has been used to generate a model of obsessive compulsive disorder (41). This model also focused to the role of goal conflict in maintaining distress, but it did not describe how the conflict would be resolved within Powers' (9) theory. It also suggested that there could be a "faulty comparator" deficit at the heart of the condition. There are a number of sophisticated neural network and robot models that test deficit models of psychiatric disorders, and that do not directly examine the process of psychological change that would occur within therapy [e.g., (42, 43)]. In particular, given the heritage of Lewis et al.'s (42) robot within Pitman's (41) use of PCT, it provides a good embodied grounding for future research that might model the resolution of conflict through reorganizations.

The concept of conflict, and conflict resolution *via* insight, has its origins at least as far back as the early psychoanalytic theories (44, 45). Indeed, computational psychoanalysis has formed its own recognizable discipline (46). However, unlike PCT, the original psychodynamic theory does not provide the formal structure required for computational modeling, and later formalisms are used for computational modeling. Yet, in contrast to psychoanalysis, conflict has had an operational definition within PCT since its inception (7, 8), as the specification of opposing reference values for the same perceptual variable; PCT also provides a specified hierarchical architecture, the mathematical specification of its components, and the learning algorithms to model how conflict is resolved, as we elaborate below. It is these kinds of conflicts that are target by a therapy based on PCT, known as Method of Levels (47). Yet, according to PCT, all effective psychological therapies work through resolving conflict, but to varying levels of efficiency (12).

Conflict cannot be solved merely by helping a person to control. The above clinical examples illustrate that actually, both sides of a conflict may be important and worthwhile to the individual—to be a strong person and to be safe; to stay sane and to get justice (see **Figure 2**). The conflict cannot be solved by helping to promote one side. Something novel and innovative needs to occur. This is where reorganization comes in. Powers and colleagues (7) adapted an idea from an early cybernetics pioneer (48) and applied it to the PCT model. When loss of control is experienced for any length of time, it engages a system that creates trial-and-error changes to the properties of the control system in error. In order to resolve conflict, these changes need to be directed not at the two goals in conflict, but above them, to the higher-level system that is setting the reference values for the two goals. So, for example, the client who is in two minds about whether to face their fears or continue to avoid them, may ultimately, be trying to be a good husband and father by staying safe and avoiding threat, and by being strong and facing fears over time.

Reorganization is also the fundamental learning algorithm in PCT. Outside PCT, learning is typically modeled as associative learning or reinforcement learning. Within associative learning, stimuli in the environment are associated with one another when they have a temporal or contingent relationship with one another. Within reinforcement learning, specific behaviors are reinforced when they lead to increased reward or reduced punishment or aversive experience in a pattern known as the reinforcement schedule (49). There are highly reliable relationships between responses and the reinforcement schedules being used in a given experiment (50). From a PCT perspective, this is to be expected because the organism is attempting to maintain the intake of sustenance at the preferred reference level. Crucial to this from a PCT perspective is that it is not the action that is reinforced but the perceptual effects of action that the organism seeks to maintain. Marken (51) used an experimental set up where bar pressed away from the goal were equally likely to those toward the goal (i.e., all responses were equally reinforced). Crucially, responses became more likely as goal progress deteriorated, regardless of the specific consequences of each action. Similarly, research on body movements shows that preferred distance can be achieved by flexion or extension regardless of the specific muscle movements involved (52). Actions must vary rapidly when changes in the environment occur which alter the effects actions have on the environment [e.g., using a reversal learning task; (53)]. When such changes in the reinforcement schedule occur, behavior has to vary

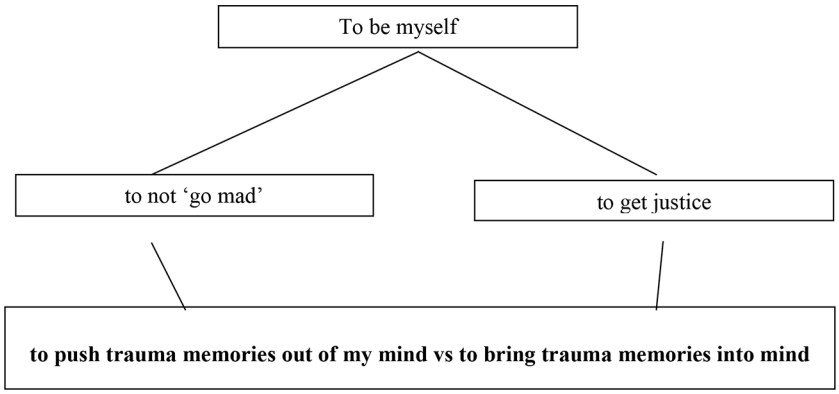

FIGURE 2 | A diagram to illustrate the three levels involved in the loss of control due to unresolved conflict according to PCT. The top level contains a single higher level system that sets two or more subgoals at the middle level. These subgoals send out conflicting references for a low level system that entails loss of control and instability —in this case, the recall and suppression of trauma memories. Note that this model is simplified—there will be control systems intermediate between the "mid" and "low" level, such as to "to be able to describe my trauma" and "to be a credible witness", as a means to achieve justice through the recall of trauma memories.

to ensure the preferred intake of sustenance is maintained. In these circumstances, PCT utilizes a learning algorithm known as reorganization. It works by generating random changes in the parameters of control systems when error is sustained, until the error is reduced to a near zero level (see later for more detail). Behavior changes are observed during reorganization but no specific stimulus-behavior associations are reinforced. Nonetheless, the results of reorganization modeling lead to the observations that most other researchers would describe as instances of reinforcement learning (54, 55).

PCT proposes a specific pathway to the resolution of conflict in practice, mediated by the focus of awareness. A client is given the opportunity to talk about a problem. It is assumed that what a client talks about is what is currently the focus of awareness, and that significant, enduring error attracts awareness. Next, it is proposed that while focusing on this problem, awareness shifts to the "mid-level" goals in conflict that are responsible for this lower level problem. The therapist can aid this process through asking about disruptions indicating transient shifts in awareness as the person is talking. Finally, and importantly, it is proposed that awareness shifts and sustains on the high-level goal (or control system) that is setting the two incompatible mid-level goals. Once here, the therapist's job is to help the client stay at this higher level while reorganization has its effects. Because reorganization operates through trial-and-error, it takes an unspecified amount of time, and it may make changes that do not improve control, until it ultimately reaches a higher level organization that resolves the conflict and improves control, thereby reducing distress. **Figure 2** shows an example of how goal conflict can be represented at three levels.

The above account is detailed, verbally described, and somewhat linear in nature, going against some of the recommendations we had in mind for the future of psychotherapy research. Indeed, we have published studies that support the above account, but they are based on subjective, observer coding of the current focus of awareness in patients receiving Method of Levels (56, 57). So, the question remains, could such a sophisticated process, based on these four principles, be testable through computational modeling? We will first describe how these principles have been tested in isolation, and then how they have been applied together to more directly emulate psychological change.

OVERVIEW OF THE METHODOLOGY AND IMPLEMENTATION OF PCT COMPUTATIONAL MODELS

The methodology and implementation of the computational models informed by PCT can be classified in various ways as one moves from principle to practice. These features are described and reviewed in detail for models of manual tracking in a recent systematic review (58).

First, there is the question of whether the validity of the model is judged by (a) its qualitative similarity to real-world data, (b) its quantitative fit with real-world data and (c) its superior fit to real-world data compared to a model informed by a competing theory. In the sections to follow, we introduce some examples of (a), many examples of (b), but very few studies have tested (c) comparative validity.

Second, there is the question of which elements of PCT are incorporated into the model. In most instances, the models involve all of the functions, signals and quantities shown in **Figure 1**. Some are often more detailed however; for example, the delays of signals as they permeate around the loop may be incorporated, and the *output function* may involve a gain (amplification), a slowing function (such as a "leaky integrator") and other transformations to create the current output quantity. Many computational models also involve further elaboration going beyond the simple control unit—hierarchies, conflict, and reorganization are not shown

explicitly in **Figure 1** and yet they form key components of the theory (9).

Third, there is the question of which software is used to carry out the modeling. The platforms vary widely and so we reference here some key examples for further reading. First, some of the earliest models were essentially algebraic equations [e.g., (30)]. Later, models used the "function" property of excel spreadsheets to make iterative computations (59). Some groups of researchers have used visual model-making platforms such as Vensim (32), or they have created visualizable models through programming code, such as C++ (54) or Matlab (33, 58). Finally, there bespoke platforms that have the workings of a control unit pre-specified, and the user creates a connected network of these units and specifies the parameters. An example of a bespoke PCT platform will be introduced later in this article.

SEPARATE COMPUTATIONAL MODELS OF HIERARCHIES, CONFLICT, AND REORGANIZATION

An earlier article summarized a number of computational models of each of the principles we have described (2). First, there are a number of PCT models that utilize a hierarchical organization to model the control of physical variables. An early study utilized a two-level hierarchy to model how human participants controlled the relative distance of two lines on the screen using two control handles (60). These movement of the cursors utilized by these models was highly correlated with the movements made by human participants, at a level close to r = .99. A hierarchical model involving four levels has been used to simulate the balancing of an inverted pendulum (61). Both of these studies show the utility of hierarchical control, but they do not show that it is necessarily superior to control without a hierarchy in modeling human behavior. Within our research group, we have produced initial evidence that this may be the case. We designed a model of visual manual tracking that required two levels—the control of proximity of a cursor to a target was achieved by setting reference values for the velocity of the cursor (62). We then optimized a different model to each of 24 participants' data, and compared the fit to a single layer, position control model. The hierarchical model was superior in fit to a non-hierarchical proximity control model when the target moved in a predictable (sinusoid) pattern, but similar in fit with a less predictable (pseudorandom) pattern. Most recently, we have confirmed that the PCT hierarchical model of the inverted pendulum within a robotic device shows superior balance in the presence of disturbances compared to two other popularly used (non-hierarchical) controllers for the same robot (63).

A number of authors have modeled conflict to illustrate its properties, and point to parallels in everyday human behavior [e.g., (34, 54, 64, 65)]. For example, Carey (34) used models of individual PCT agents initially designed to illustrate crowd behavior [e.g., (66)]. One of these agents, A, had a goal to move to a fixed location but to stay away from another agent, B. B had a goal to get close to A. Carey (34) explored the effects of a parameter known as *gain*, which is effectively the effort put in to achieve one's goals. At low levels of gain in both agents, there was no evidence of conflict, with both agents reaching their goals. However, when the gain of B was increased, A could not reach its goal because it was blocked by B. This could illustrate the suppression of one goal (e.g., to never feel angry) by another (e.g., to express one's anger). If, in turn, the gain of A was increased, the two agents oscillated widely and vigorously, potentially illustrating the loss of control that can come from increasing one's efforts. The remaining studies of conflict have not interpreted their findings in the context of psychological distress, but either in terms of social group behavior (63, 64), or to illustrate more universal principles (54).

An early model of reorganization illustrated that it followed a similar principle to that used by human participants to reach a goal when only the timing of a trial-and-error change in behavior could be controlled (66). Probably, the most sophisticated computational models of reorganization published to date illustrated how it reduces conflict and improves control within a simulated model of an arm with 14 independent control systems governing the movement at joints (54). At the start of the simulation, the control systems interfered with one another. However, after a period of reorganization in which the gain of each system is reset randomly when error across the whole arm increases, they each converge to a gain that counteracts any disturbances from other joints, and the whole arm is able to smoothly execute its movement—one that Powers selected from Tai Chi.

Powers (54) clearly illustrates the capacity for reorganization to reduce error, but no attempts were made to quantitatively test this model against real-world behavior. There are some key parallels between observations of the trajectory of change that is observed in models of reorganization and those observed in studies of psychological therapy. The first is that the change trajectory observed in psychological therapy follows a *negatively decelerating* curve (67), which means that change is more likely to occur earlier in therapy than later. One early meta-analysis (68) suggested that given 75% of patients required 26 sessions for a successful outcome, this was a "rational" time limit. However, it is explicit that 75% of patients do not require this amount of input. Indeed, others have observed that therapy gains are greater in earlier sessions (69). Furthermore, this has led to the suggestion that change is nonlinear, dynamic and complex (70). However, the conclusion that change looks complex does not mean it is generated by a complex system. Indeed, the simulations reported by Powers (54) contain very few systems interacting; yet, each iteration of a simulation generates a different pattern of change, and takes different periods of time to achieve stability.

As already noted, gains in therapy are most often observed early in therapy (71). They also follow a discontinuous pattern, appearing suddenly and unexpectedly in many cases. This has been reported in naturalistic settings (72) and experimental studies (73). One approach to psychotherapy change is the dynamic system approach (74) that describes how client-therapist dyads produce new information that results in the

"reorganizing of behavior", which can occur suddenly. However, the algorithms underlying this model are arguably not straightforwardly linked to psychotherapy change, as the putative variables in the model are therapist interventions or working alliance, which are distal to the client experience of distress. The PCT account of therapeutic change considers chronic error, maintained by conflict, to be the crucial variable to simulate in modeling.

The PCT account of psychological distress is key for developing a parsimonious method of implementing computational models of psychotherapy change processes. The core trans-diagnostic process of conflict maintaining error across disorders has a clear implication: it means that a single approach to modeling can be used across the themes that people describe as problematic (e.g., isolation, evaluation of others, contamination, or maintaining weight). The account of psychological distress described above points to chronic error (loss of control) as crucial to understanding the underpinning symptoms. On this basis, all varieties of symptoms can be thought of as expressions of chronic error and, for this reason, simulations based on PCT principles generate a fundamental indicator of outcome—the magnitude of chronic error. If error is equivalent to psychotherapy outcome, simulations can be used to compare real-world therapeutic outcome with simulations based on PCT and this may be done across diagnostic categories.

As noted earlier there are some well-established findings in the psychotherapy literature of the trajectories of change, such as early gains, sudden gains, and the negatively decelerating curve. If error can be equated with outcome then it is possible to compare these patterns of outcome with the trajectory of change generated by models based on PCT principles. The model that provides a starting point for this investigation is the "trial-and-error" process described by Marken and Powers (66). The "trial-and-error" process is acknowledged to be fundamental to psychotherapy, as therapists are responsive to interventions that are ineffective by moving to new strategies (75). However, it is rarely acknowledged that clients are also exploring their mental life in therapy sessions, generating new perspectives and solutions; this is central to the PCT account of psychotherapy change. However, the implications of "trial-and-error" exploration for the trajectory of psychotherapy outcome have not yet been examined.

As already noted, the simplest starting point is to assume their symptom score at each session expresses the client's current state of error. Each session is assumed to provide an opportunity to reorganize goals and generate novel solutions that reduce chronic error. The simulation of iterative episodes of reorganization has already been implemented in the PCT model described by Marken and Powers (66) and can be arranged to simulate changes in an outcome measure during successive sessions in psychological therapy. Like Marken and Powers (66), the model of therapy change can simulate successive iterations of reorganization with each iteration taken to reflect a "session" with severity of symptoms carried over from the last. The model can be set up so the output of the system changes to a greater extent when error is highest and less when error is lower. The output of the system would be analogous the activity people engage in when controlling a perception of, for example, a sense of connectedness to others. Thus, exploration is greatest when error is high. However, the exploration may be focused on a specific perspective on the problem, for example, thinking continually about how a social interaction might have gone differently so that humiliation did not occur. The forgoing account of the change process of therapy suggests that people can be helped to direct this exploration to higher-level perceptions.

This verbal account of therapy can be cast as a computational model where exploration is conceptualized as a trial-and-error process constrained by the degree of error. On each "session", the there is a reference value for a desired amount of symptoms (zero), and this is compared to current symptoms to generate an error signal. This error signal tunes the amount of random change in output (or behavior), greater error results in a higher chance of change in the system and vice versa. The output then has an effect on the environment that is either perceived as being either closer, or further, from the desire state of the perception and so another error signal is generated. In the model, error signal is taken to reflect the level of "symptoms" and this is standardized to a clinical dataset to observe the trajectory of change produced. **Figure 3** demonstrates a simulation of CORE 10 scores in N = 5,613 "cases" based on a starting point of the level of severity of symptoms taken from data reported by Stiles et al. (71). As can be seen in **Figure 3**, change is more likely early in the change process simulated by the model than later, generating the negatively decelerating curve described previously.

COMBINED COMPUTATIONAL MODELS TO SHOW THE REORGANIZATION OF A HIGHER-LEVEL CONTROL SYSTEM RESPONSIBLE FOR CONFLICT

While it is persuasive to see the qualitative parallels between the behavior of models of principles, such as conflict and reorganization, and the pattern of change in psychological

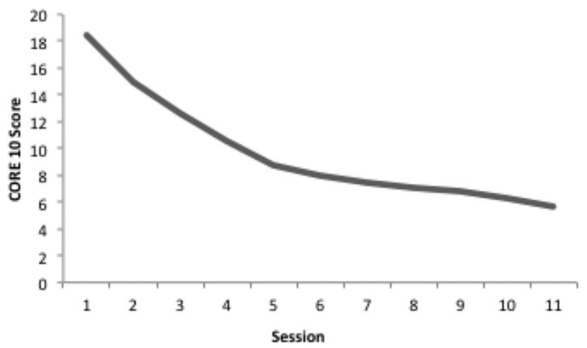

FIGURE 3 | The trajectory of CORE 10 scores for a simulation based on the principle of reorganization. Original figure.

distress, it does not directly test the specific mechanism thought to mediate change according to PCT. There are two steps in this advancement. First involves constructing a hierarchical model in conflict that regains control through reorganization of the higher-level system setting the two (or more) conflicting subgoals. Second involves constructing and optimizing these models for individual human participants and testing them against the real-world data as each participant experiences psychological change in therapy. Our research group has made significant progress with the first stage, and we are building the elements to carry out the second stage over the coming years.

In order to complete the first stage, we developed a bespoke software platform using C++ to allow the user to construct hierarchies of control systems that could be prone to conflict, and that could employ reorganization (76). The coding for this software is available from the first author, and second bespoke platform is also available from perceptualrobots.com.

Our first study tested whether allowing reorganization allowed two goals in conflict to regain control. It also tested the key prediction of a PCT model of psychological change—whether the restoration of control was more effective if the reorganization was directed at the higher-level goal setting the goals in conflict.

The control systems were constructed such that they would simulate the parallel processing that occurs in the nervous system, and they were refreshed every 16ms to allow dynamic updating to occur across all systems simultaneously. The experimenter optimized the parameters for each of the components of a single control system (e.g., gains and disturbances) so that this unit could control a single variable. Next, two higher level systems were now added to set the reference value for this system; the relative weighting (connection strengths) of these two systems in setting the lower level reference value was set randomly for 20 different agents. Next, a third level system was added to the top and it had two outputs—one setting the reference value for each of the two mid-level units. Again, these two connection strengths were set randomly for each of the 20 agents. In these simulations, reorganization worked by selecting a new direction and value of change in connection strength that was proportional to increase in cumulative error (loss of control) over a specified time window.

The study tested the degree of restoration of control in three different conditions: no reorganization; reorganization of the mid-level systems; and reorganization of the higher level system. Akgonul (76) found, as predicted, that the agents who could reorganize regained more control, and that this effect was stronger when reorganization was limited to the higher-level system. This finding was replicated using the same platform in another study (77). The graphs of individual agents from this study also reveal the patterns of observed change in psychological therapy described earlier—the early response pattern, and sudden gains during therapy (see **Figure 4**). Thus, from a qualitative perspective, the PCT simulation shows similar patterns of psychological change to those that have been identified within individual patients.

A ROBUST COMPUTATIONAL MODEL OF PSYCHOLOGICAL CHANGE ACCORDING TO PCT

In order to prepare for the second stage and test a PCT model of psychological change against real-world data, a number of steps are required: (a) to identify an experience of psychological distress for which a clinically meaningful controlled variable can be easily measured, and for which a change would be expected after therapy; (b) to construct a simulation of the conflicted control systems governing this variable that can reorganize in the way specified by PCT; (c) to build this model and optimize it for individual participants; (d) to test the optimized models of individuals against the real-world data both before and after therapy.

We have selected spider phobia as the psychological problem to investigate. It is common and therefore easy to recruit, and the source of distress is relatively more circumscribed that other anxieties. Furthermore, it is commonly accepted that the distance that a person with spider phobia is willing to stand from a spider is an appropriate index of their difficulties that reduces with effective treatment (78). Yet, the control theory perspective on approach and avoidance differs from the behavioral perspective in explaining this process (see **Figure 5**). Specifically, "approach" and "avoidance" are not regarded as learned responses to the "stimulus" of a spider. Rather, according to PCT, the individual attempts to control a range of perceptual variables that are relevant to spiders, one of which is likely to be the desired distance. The same individual can have two discrepant desired distances from the spider. First, the defensive distance keeps the spider at a distance perceived to be sufficiently safe, and a second, closer distance, is set by higher level systems for goals such as "to recover from my phobia", "to be strong", or "to enjoy being in the garden". Thus, what appear to be discrete, triggered behaviors to approach or avoid a stimulus are actually the oscillations between two conflicting perceptual set points—one close to, and one far away, from the feared entity—the spider in this example.

Note. Traditional paradigms present a threat stimulus and measure whether avoidance or approach is triggered in the participant. A control theory perspective regards approach and avoidance as the observable consequences of an individual who has conflicting goals regarding their desired distance from an object in the environment (that may or may not be feared). Critically, when the defensive distance is greater than the distance required to fulfill another important goal (e.g., to overcome their fears; to spring clean their house; to return to work, etc.) the person maintains a compromise distance and any oscillation in behavior at each moment appears to the observer as either approaching or avoiding the object. Relatively strong fears in the context of weaker approach motivations would involve a compromise distance that is closer to the defensive distance.

In order to assess the dynamic control of distance from a naturalistically moving spider in real time, we have developed a virtual reality paradigm in which the user can exert control over their distance from a spider in a room (see **Figure 6**). We have

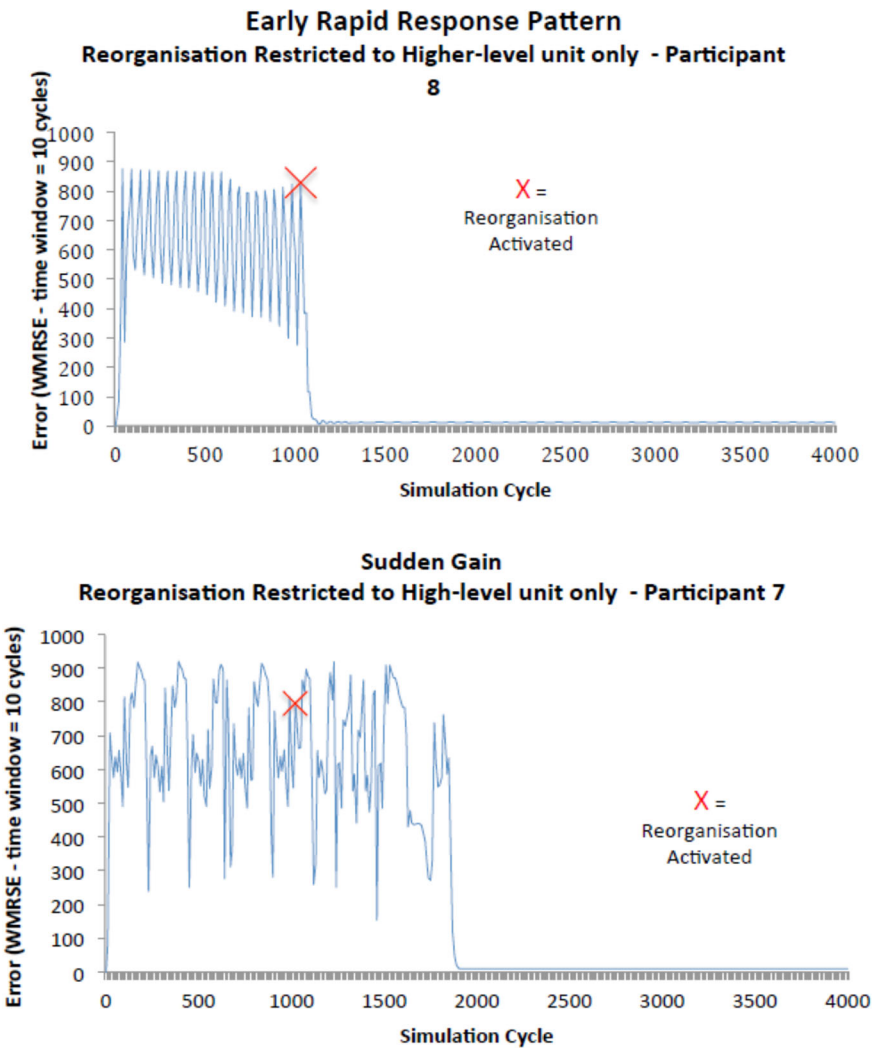

FIGURE 4 | Graphs of change in overall error during the simulation in individual agents. The first pattern resembles the early response pattern found in patients, and the second pattern resembles sudden gains during therapy (77). WMRSE is the Window Mean Root Squared Error. To calculate WMRSE, the squared error terms across all control units are averaged over ten iteration cycles of the simulation, and then the square root of this figure is calculated.

also developed a goal interview to allow each participant to report the importance of their conflicting goals with respect to their goals to be far away from the spider versus to be close to it (27). This interview also estimates the extent to which people with spider fears are aware of their goal conflict. There are also ways to attempt to assess goals and their conflicts using measures such a goal matrices (80) and repertory grids of personal constucts (81).

We plan to construct a separate three-level hierarchical model for a large number of individuals with widely varying fears of spiders (see **Figure 7**). The initial gains for the control systems in conflict will be approximated as the importance ratings from the goal interview. Then each hierarchy will be optimized to each individual by training it on dynamic spider-distance data within the virtual environment over a fixed session length. In the first test of the validity of the model, we will measure its fit for each participant to the movements in a second VR session, thereby assessing the individual specificity of each model (33). Because goal conflict is likely to occur in some participants, the kind of exact match to behavior observed in tracking studies will not be possible for every individual. Nonetheless, there will be ranges of parameters for which behavior will be more predictable, for example where one goal has a much higher gain and therefore dominates the control of distance from the spider.

After establishing individual specificity, we aim to test the PCT model of psychological change. As in Akgonul (76) and Cooray (77), each hierarchy will be programmed to have the capacity to reorganize. Owing to the stochastic nature of reorganization, it will not be possible to assess the model fit against moment-by-moment behavior. Therefore, our aim is to

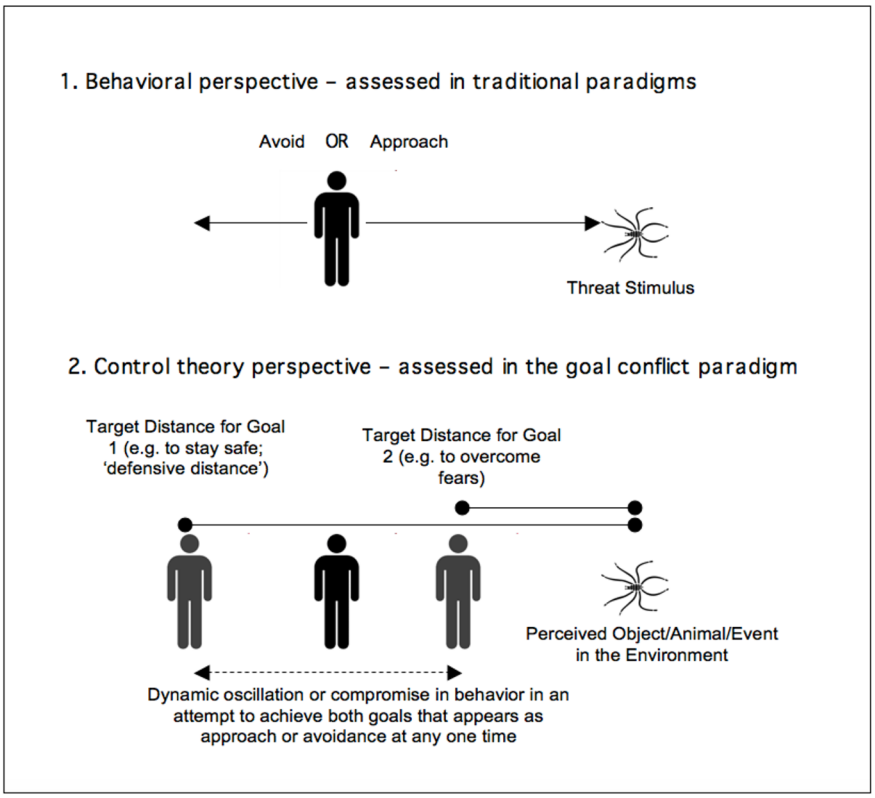

FIGURE 5 | The behavioral perspective on avoidance contrasted with the control theory perspective (79).

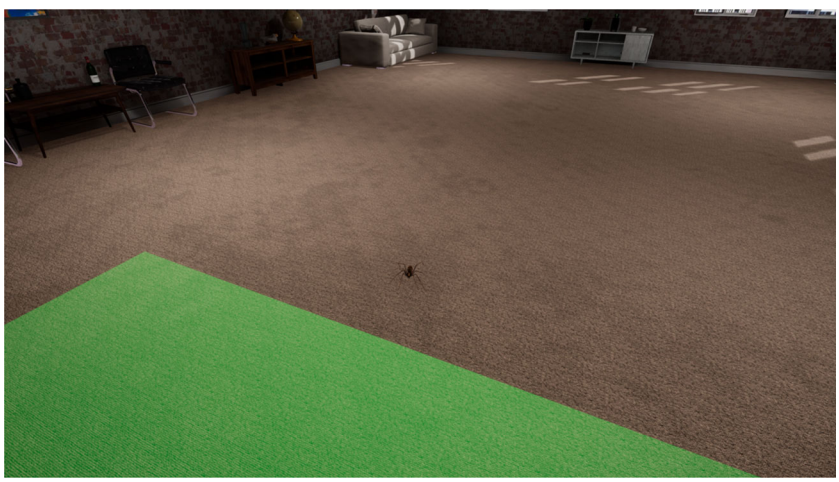

FIGURE 6 | A static screenshot from the virtual reality environment within which each participant can control their distance from a naturalistically moving spider. Original image.

show whether incorporating reorganization into the model can demonstrate the patterns of change that are shown within spider-fearful individuals who are exposed to the spider within VR; namely, the sudden reduction of distance from the spider after reorganizing the higher-level goals driving the conflicted systems. Indeed, our previous research has shown that people who report greater awareness of goal conflict extracted through an interview tend to approach closer to a spider after an exposure session (40).

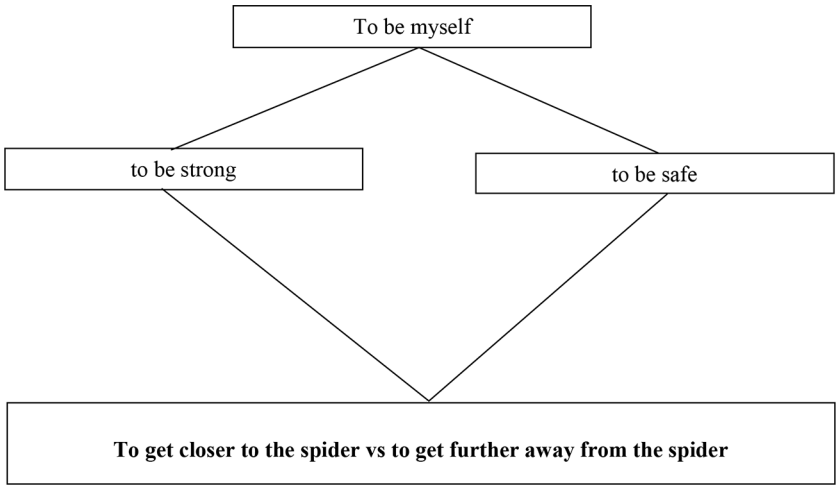

FIGURE 7 | A simplified diagram of the three-level hierarchy involved in spider phobia. The fearful individual fluctuates in their distance from the spider depending on whether they are acting "to be strong" and get closer, or "to be safe" and get further away. However, when the same individual is provided with the opportunity to talk about their conflict and shift and sustain their awareness to the level setting these goals—"to be myself"—this permits trial-and-error reorganization of the higher-level system (e.g., sets different gains for each of the mid-level goals) such that the conflict is reduced and control increased.

Therefore, we will optimize a reorganization parameter within the model of each participant to assess whether it can lead to the same pattern of approaching closer to the spider after the goal interview that we record in participants.

LIMITATIONS, EXTENSIONS, AND FUTURE DEVELOPMENTS

We have described our plans to test a simplified model of psychological change based on PCT. At present, it omits a number of features that are nonetheless known to be involved in psychological therapy and whose function is specified in PCT. These are: the biological (intrinsic) control systems within the individual; the physical environment within which action occurs; the therapist (for a diagrammatic PCT model of the therapy dyad, see 82); memories as perceptual goals (83); awareness (47); and communication through language (84). Therefore, there still remains a wide chasm between the details of a theory that can be described, and the extent to which all of these can be reproduced together within a faithful working model.

One novel solution to this issue is to use human actors to simulate individual clients before, during and after therapy in a manner similar to Stanislavski's method of training actors [(85); Scholte, personal communication]. This method involves inferring a person's multiple goals and their conflicts, acting according to them within a situation, and revising these goals iteratively to steadily improve the match to the script, or, in this case, the real-world behavior. This approach has advantages in terms of the potential complexity of goals that can be modeled, but it is clearly not specified computationally, nor can it provide robust tests of how the principles of a theory operate (e.g., reorganization).

This issue raises a further question around mechanism—not only is it important to test a functional model of the change process, but it is also necessary to test whether the human brain can implement this process, and if so, exactly how. There is likely to be a specific neuranatomic circuit involved in this process of resolving conflict: identification of conflict *via* the anterior cingulate, and two cortical structures—the ventromedial frontal cortex and orbital frontal cortex—that appear to be involved in evaluating the appropriate decision during goal conflicts [e.g., (86)]. However, a realistic neural model of this process that maps onto the PCT architecture we have described remains a future challenge.

The approach we have described has potential for areas of research into human behavior that extend beyond psychotherapy. For example, Bowlby's attachment theory involves a conflict between exploration and safety-seeking, which can be specified as perceptual goals. It comes much closer to PCT because it is based on control systems theory, it involves interpersonal dynamics, and its internal working models are essentially hierarchical and conflicting control systems (87). The use of robots to model the dynamics of child-caregiver interactions in earlier studies [e.g., (88, 89)] could be extended to the interactions between therapist and client during exposure, for example, and could be optimized to test against behavioral data from humans. The fields of social and personality psychology have also touched upon dynamic modeling, but could be expanded upon (90). It is also feasible that research on robotics could eventually utilize and test PCT models of psychological change, involving memory and learning, following promising work on simulating navigation and locomotion (91).

SUMMARY

We have described a novel and sophisticated methodology to test the mechanism of psychological change within psychological therapies. This approach requires the construction of computational models that attempt to directly emulate the psychological mechanisms occurring within each individual client. We summarized the evidence to date, which is consistent with a PCT account of psychological distress as chronic, unresolved goal conflict held outside awareness. However, a robust evaluation of this model requires a long-term research program that is currently in progress. It is our view that researchers need to become acquainted with this methodology and to start to develop the skills and resources to use it, because it provides a feasible way to properly "understand the engine" of psychological change, and how best to engage and harness it within clinical practice.

AUTHOR CONTRIBUTIONS

WM conceived of the review and organized the structure and main argument, and WM and VH produced the content.

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