

## Review

# Clinical and methodological considerations for psychological treatment of cognitive impairment in major depressive disorder

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## Background

Cognitive impairment is considered a core feature of major depressive disorder (MDD) and research into psychological treatments aiming to address cognitive impairment are gaining momentum. Compared with the well-established research base of cognitive treatment trials in schizophrenia, including meta-analyses, mood disorder research is much more preliminary.

## Aims

To focus on identifying the important factors to consider in developing larger-scale psychological treatment trials targeting cognitive impairment in mood disorders. Trial design recommendations have been published for cognitive treatment trials in bipolar disorder.

## Method

An in-depth discussion of methodological considerations in the development of cognitive treatment trials for MDD.

## Results

Methodological considerations include: screening for, and defining, cognitive impairment; mood state when cognitive intervention begins; medication monitoring during cognitive interventions; use of concomitant therapy; level of therapist involvement; duration and dose of treatment; choice of specific

cognitive training exercises; home practice; improving adherence; appropriate comparison therapies in clinical trials; and choice of primary outcomes.

## Conclusions

As well as guidance for clinical trial development, this review may be helpful for clinicians wanting to provide cognitive interventions for individuals with MDD.

## Keywords

Depressive disorders; cognitive function; cognitive remediation; clinical trials; psychological treatment.

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Preliminary research suggests that cognitive activation (also referred to as cognitive training) and cognitive remediation treatments may be helpful for patients with major depressive disorder (MDD). A variety of studies have been undertaken, mainly with relatively small sample sizes, yielding only preliminary results at this stage. These studies have also provided evidence regarding methodological issues, particularly those that may result in failed trials. It is therefore timely to review methodological issues in studies of cognitive activation or remediation in MDD and to provide recommendations for future trials. We note that expert papers and reviews of methods have been published from the cognitive remediation literature for bipolar disorder and for schizophrenia. For example, an expert group has provided recommendations for clinical trials examining treatments that may enhance cognitive function in bipolar disorder.<sup>1</sup> Miskowiak et al's paper reviewed trials in bipolar disorder only and referred to both pharmacological and psychological treatments.

The current paper examines psychological treatments for cognitive function in more detail, and specifically in MDD. We will not refer to treatment studies of social cognition training in MDD, as this area is a very new area of research, and findings much more preliminary. 'Cognitive treatment' or 'cognitive interventions' will be used as an all-encompassing term throughout this paper to refer to strategies using cognitive activation and/or cognitive remediation approaches.

Although this paper is intended primarily for researchers engaged in cognitive treatment trials, in the absence of evidence

of effectiveness of specific treatments for cognitive impairment in mood disorders,<sup>2,3</sup> some clinicians may choose to attempt to provide patients with cognitive practice schedules and remediation strategies. Some of the material in this paper may be helpful in guiding this endeavour.

## Overview of cognitive treatment approaches

Cognitive activation versus remediation

There is a difference in the breadth of treatment procedures between an activation approach and a remediation approach.<sup>4,5</sup> The former involves repetitive and regular practice of cognitive exercises in order to activate specific parts of the brain that are underactive in MDD. Compared with a cognitive remediation approach, a cognitive activation approach focuses much less on strategy coaching for cognitive exercises and on generalising gains made in cognitive exercises to everyday life. As an area of future study, it will be important to determine if cognitive activation is likely to be more useful during episodes of major depression (see Fig. 1), when brain changes are those of the active disease state. Exercises should then be targeted towards this aim and may involve utilising cognitive exercises that have been shown in functional magnetic resonance imaging paradigms to activate particular parts of the brain.

It is beyond the scope of this paper to discuss this in detail beyond noting that preliminary studies have suggested that, for instance, the Paced Auditory Serial Addition Task practised in a



**Fig. 1** A testable hypothesis: cognitive activation versus remediation based on mood state.

Activation would be delivered during an acute depressive episode; remediation would usually be delivered after remission from a mood episode. Under the horizontal line represents low mood, and moving from left to right represents time course of mood episode.

repeated way has been shown to activate dorsolateral prefrontal cortex (see the Neuroimaging findings in cognitive treatment trials section).<sup>4</sup> Preliminary evidence suggests benefit on outcomes other than cognitive function during major depressive episodes, using this type of approach, including reduction in depressive symptoms and rumination,<sup>6</sup> yet evidence for transfer to improvements in everyday functioning are lacking.

In cognitive remediation studies, techniques go beyond cognitive activation to include a substantive role for a therapist to help the patient develop new strategies for problem-solving and facilitate the transfer of cognitive gains made in computerised training to 'real-world' situations. Remediation may be broadly aimed at improving global cognitive function and general functioning, or it may be targeted at specific deficits that patients experience. The tasks used and the difference between specific (for example memory training) versus global (for example spanning all cognitive domains) remediation may also depend on whether the remediation is being delivered individually or in a group format. In some settings, patients self-select exercises and their difficulty levels. Another way of achieving targeted remediation is to analyse detailed cognitive testing at the beginning of treatment and explicitly to target impaired areas.

### Three pillars of treatment

The three pillars of treatment are computerised cognitive training, strategy monitoring and transfer of cognitive change to functioning.

#### Computerised cognitive training

Computerised cognitive training exercises entail drill and practice procedures for training cognitive abilities, including those that are lower order (such as attention, processing speed) and higher order (such as working memory, visual memory, verbal memory and executive functioning). These exercises should have numerous difficulty levels, wherein the complexity of the stimuli presented titrates in an increasing fashion, based upon the patient's performance. In this way, individuals are presented with a sufficient level of challenge, but ideally not so difficult as to decrease engagement or deter participation (for more discussion on task difficulty, see the section entitled Level of difficulty and feedback on performance).

Typically, exercises are game-like in nature and provide the individual with feedback on accuracy, and sometimes efficiency, of performance. Via repetitive engagement in these drill and practice cognitive training exercises, the goal is for activation of neuronal networks associated with cognitive deficits, resulting in brain neuroplasticity, leading to tissue growth<sup>7</sup> and greater efficiency in neurophysiological processing.<sup>8</sup>

#### Strategy monitoring

Strategy monitoring introduces the notion of metacognitive awareness and monitoring of one's own problem-solving skills. This

procedure differs from treatments that aim to compensate for impaired cognition, where strategies provide opportunities to 'work around' a deficit. In contrast, in cognitive remediation, the goal is to build new strategies, recognise which strategies might work given the situation, and develop skills to flexibly switch strategies as an adaptation to shifting environmental demands. In treatment, therapists work with patients to become aware of their typical range of problem-solving approaches while performing cognitively demanding activities. Individuals with MDD often lack insight into their cognitive performance, with a disconnect between subjective and objective assessment of performance.<sup>9</sup> They may be indecisive or withdraw from cognitively complex tasks.

Within the treatment session, individuals are encouraged to monitor and identify the strategies that they employed while practising the computerised cognitive training exercises. The ability to monitor one's own cognitive processes (i.e. metacognition), is an important predictor of the degree to which individuals with mental illnesses use their thinking skills in daily life.<sup>10</sup>

Fundamental to this pillar is the ability to develop new strategies, prune ineffective strategies and flexibly shift one's strategies to best meet the demands of the cognitive task. Within a group setting, therapists facilitate the discussion to elicit identified strategies of patients. Group members can learn from one another and gain new strategies to implement during subsequent cognitive training sessions.

#### Transfer of cognitive change to functioning

One of the main goals of cognitive treatments is to ensure that cognitive gains, and the new problem-solving strategies that arise in treatment, manifest in daily life. To that end, treatments typically provide a platform for discussion with the therapist (and other patients, in group format), regarding how the cognitive skills being trained, the development of strategic monitoring and the ability to flexibly shift one's problem-solving approach, can be employed in real-world settings (for example occupational, social, household, self-care, leisure).

'Bridging' approaches, similar to those pioneered by Medalia et al,<sup>11</sup> traditionally employ discussions individually tailored to goals for everyday life. Although traditional cognitive remediation approaches demonstrate efficacy in improving cognitive function, effect size differences across studies with regards to real-world functional improvement is more variable.

Within the psychosis literature, cognitive training paired with additional skills acquisition opportunities (for example vocational training or psychosocial rehabilitation) improves the likelihood of transfer of effects of cognitive remediation to everyday behaviours.<sup>12,13</sup> In light of this, an approach that integrates simulated real-world tasks and role-plays into the treatment has been developed.<sup>14</sup> In this approach, action-based cognitive remediation treatment integrates procedural learning skills and advances the process

of abstraction in bridging through the use of simulated activities that provide an in-session opportunity for individuals to apply their problem-solving techniques generated via strategy monitoring. This approach integrates goal-setting and behavioural activation procedures to help participants identify their real-world goals and small steps to take towards achieving them.

In MDD, action-based cognitive remediation has shown significantly better retention rates, greater increases in perceived competence with cognitively challenging tasks and significantly improved functional competence relative to traditional cognitive remediation approaches.<sup>14</sup> Further, those in action-based cognitive remediation are more likely to be competitively employed following treatment and experience less job-related stress.<sup>14</sup>

## Methodological issues in cognitive treatment trials

### Screening for inclusion based on cognitive impairment

Cognitive impairment is considered to be a core feature of MDD on the basis of a substantial body of research showing moderate to large effect-size differences in group means between participants with depression and healthy controls. A percentage of patients, however, do not show significant cognitive impairment when judged by significant deviation from the 'normal'.<sup>15,16</sup> This percentage varies depending on the nature of the group being studied, mood state and the definition of 'abnormal performance'.<sup>17</sup>

The purpose of any proposed cognitive intervention, whether to activate or remediate, is important to consider prior to deciding whether cognitive screening is appropriate. Research in bipolar disorder indicates that individuals with the most severe cognitive impairment receive the greatest benefit from interventions aimed at improving cognitive outcomes.<sup>18</sup>

Inclusion of a number of patients with unimpaired cognitive function may wash out any positive effect and result in failed trials.<sup>3,19</sup> However, cognitive activation may also have positive effects on mood and therefore, be potentially beneficial in patients with milder cognitive impairment.<sup>5,6</sup> Furthermore, many patients identify as having 'subjective' impairment.<sup>9</sup> These patients may avoid cognitive challenge leading to poor functioning and ultimately a reduction in their cognitive ability. Allowing only those patients with serious objective cognitive impairment to partake in cognitive treatment trials means that the majority of patients with MDD would not have the opportunity to experience the possible activating effects on mood of repetitive cognitive training.

Trials aiming to maximise cognitive improvement with cognitive interventions in patients with predominantly euthymic mood are thus likely to screen for cognitive impairment. However, as in all clinical trials, there is a difficult balance between the imperative of the clinical trial – to produce a positive result, often achieved by selecting the most impaired patients, and the ability to develop treatments that may be effective across a range of impairment and are generalisable.

### Definition of cognitive impairment

In trials that choose to screen for cognitive impairment, consensus on the specific definition of impairment would be beneficial. Approaches used to define cognitive impairment in MDD research, and in other psychiatric and neurological disorders, vary widely. While an in-depth discussion of all possible definitions is beyond the scope of this review, the more common or feasible approaches are discussed below.

**Comparison with 'normal' level of functioning.** Degree of cognitive impairment can be assessed by comparing patients' cognitive test performance with standardised age-appropriate norms or with well-matched healthy control samples, as has been done in some mood disorder studies to date.<sup>15,16,20</sup> Using mean healthy control

group scores as references is likely to be more variable than using standardised norms. On the other hand, the use of healthy control scores as a reference may be a more accurate way of determining scores in a population of a particular age, gender and premorbid IQ, particularly when less traditional or non-standardised tests are being used in the cognitive testing batteries. In practise, there does not appear to be a clear relationship between choice of reference and prevalence rates of impairment.<sup>20</sup>

More important is the definition of impairment used. Douglas et al<sup>17</sup> highlighted this issue by examining prevalence rates of cognitive impairment using four different definitions of cognitive impairment in four mood disorder samples, compared with four matched healthy control group samples. Prevalence rates of cognitive impairment in a sample with severe depression ranged widely, from 19% when using a single cognitive composite score (1.5 s.d. cut-off), to 60% when using a definition of having a score below the cut-off (1.5 s.d.) on at least two individual test variables. Similar variability in prevalence rates was shown in the three other mood disorder samples in this paper.

**Change from previous level of cognitive ability.** A more individualised approach to determining level of cognitive impairment may be to determine the extent of change in cognitive function over time in each patient. Ideally, this would occur by assessing cognitive function prior to depression onset, and then over the course of mood episodes. This prospective tracking, however, is not realistic in clinical or research settings. Thus, reliance on measures that estimate premorbid level of cognitive functioning is the next best option.

Word reading tests, such as the National Adult Reading Test<sup>21</sup> and Wide Range Achievement Test Reading Recognition Subtest,<sup>22</sup> are the most commonly used measures of premorbid IQ or level of functioning. The value of these tests lie in the fact that word reading tends to be preserved in abnormal ageing and other neurological disorders,<sup>23</sup> and thus, can provide an accurate measure of premorbid verbal IQ.

In relation to this, Tran et al (under review; Bowie & Milanovic, personal communication, 2020) investigated two definitions of cognitive impairment in a MDD sample ( $n = 111$ ); 'idiographic impairment', defined as the neurocognitive composite score being more than 0.5 s.d. below premorbid IQ, and 'normative impairment', which reflected impairment relative to normative standards (i.e. a neurocognitive composite score that fell at least 1 s.d. below age-appropriate norms). Although approximately 25% of the participants were normatively impaired, 62% of those whose cognitive functioning was within normative limits showed idiographic impairment. Interestingly, these different types of cognitive impairment showed different profiles of association with subjective functional competence and objective functional capacity.

Similar analysis conducted by Douglas et al<sup>17</sup> in participants who were severely depressed showed vastly different rates of cognitive impairment depending on whether a normative (compared with healthy controls) or idiographic definition of impairment was used (19% *v.* 42%, respectively), with the National Adult Reading Test used as the measure of estimated premorbid IQ in the latter definition. Exploring this difference indicated that increased prevalence of cognitive impairment when taking premorbid IQ into account was because of a substantial portion of patients with above-average estimated premorbid IQ being re-categorised as impaired after correction for premorbid IQ.

The findings of Tran et al<sup>24</sup> and Douglas et al<sup>17</sup> highlight the fact that assessing cognitive function in relation to an estimated previous level of functioning can result in different individuals being categorised as 'cognitively impaired', and that the subjective experience of a decline in one's own cognitive functioning may raise negative beliefs about one's functional abilities in daily life.

Subjective cognitive impairment. Patients with mood disorders report cognitive impairment to be one of the most concerning residual symptoms between episodes, which has a great impact on occupational functioning.<sup>24</sup> Some cognitive treatment trials use subjective (rather than objective) cognitive impairment as an inclusion criteria, as those who believe that they have significant problems with cognitive function will likely be the most motivated to enrol in such trials. An issue with this approach, however, is that subjective cognitive impairment does not necessarily relate to objective performance on neuropsychological tests. This disconnect between subjective and objective assessment of cognitive performance was reported in a recent study using two samples with depression from Denmark and New Zealand (total  $n = 137$ ). In this paper, the majority of patients with depression showed disproportionately more subjective than objective cognitive impairment (termed 'sensitivity'), which was related to depression severity and younger age.

Given that a major aim of cognitive treatment trials is to not only improve cognitive function, but also general functioning, further research into how aspects of cognitive impairment correlate with general functioning is warranted. This will then clarify what definition of cognitive impairment is the most representative of difficulty in real-world settings, and may be most appropriate for cognitive remediation trials.

#### Mood state when patient begins a cognitive treatment trial

An important methodological issue is whether patients should be deemed to have recovered to a particular level prior to initiating a cognitive intervention. Once again, the question of whether the primary approach is activation or remediation is important as the former will generally be employed in patients who are currently depressed. The relationship between current mood state and cognitive function is not absolutely clear. Generally, however, the degree of, or percentage of patients, with cognitive impairment has been found to be greater in patients who are more severely depressed,<sup>17</sup> which could relate to a direct relationship between low mood and cognitive function or to the fact that greater severity and greater cognitive impairment both relate to a more biological illness. Studies should be clear regarding whether the approach used is one mainly of 'activation' in patients who are currently predominantly depressed or 'remediation' in patients who are more recovered but who are cognitively impaired.

#### Medication monitoring throughout cognitive treatment trials

Changes in medication during cognitive treatment trials may be important confounders of the effects of the experimental treatment. For example, in trials of cognitive activation for patients in episode, medication may be more actively changed in the control group because of poorer clinical response. This might obscure a benefit of cognitive activation. In trials of cognitive remediation, ongoing poor cognitive function might prompt the use of possible pro-cognitive drugs such as vortioxetine,<sup>25</sup> which may mask a benefit for the active treatment. In order for trials to be pragmatic, medication changes based on clinical need should be allowed during the protocol – however, these changes should be analysed between groups as part of the assessment of outcomes.

#### Concomitant therapy in cognitive treatment trials

Meta-analyses on the effects of cognitive remediation in schizophrenia<sup>12</sup> have shown that effects are greater if cognitive remediation is combined with adjunctive rehabilitation therapies, such as social skills/social perception/social information processing training, and vocational rehabilitation. Thus, in MDD, in order to confer an effect on wider functioning, particularly occupational functioning, it may be advantageous for cognitive interventions to be combined

with some form of occupational therapy or rehabilitation. This has been trialled in action-based cognitive remediation in treatment-resistant depression, with positive preliminary results.<sup>14</sup>

In general, little evidence exists to suggest that traditional psychological therapies on their own have a beneficial effect on cognitive function in mood disorders.<sup>26,27</sup> However, one preliminary study of metacognitive therapy for MDD suggested a positive effect specifically on cognitive function.<sup>28</sup> This may have been related to the fact that this therapy incorporates a specific cognitive training component (attentional training technique) that could in fact have been classified as a cognitive treatment.

#### Level of therapist involvement

There are varying levels of therapist input in cognitive interventions, including exclusively online computer training, some supplemental online therapist input to complement online practice, and other therapy formats offered within individual or group therapy sessions with clinicians.<sup>5</sup> Formal comparisons of these methods are lacking; however, Porter and colleagues<sup>5</sup> discuss relative strengths of each, whereby largely independent treatment without clinician input has the benefit of low cost. In contrast, for severe mood disorders, skilled therapists may be especially helpful in assisting patients in their valuing of, motivation to engage in, and working through barriers hindering engagement in, the treatment. Further, although cognitive treatment programmes relying exclusively on drill and practice with minimal therapist involvement tend to result in neuroplastic changes, transfer of skills to everyday functioning is not observed.<sup>29,30</sup> Thus, the role of the therapist may be particularly important for extending neurocognitive gains to functional improvement.

Varying levels of therapist involvement might be warranted over the course of treatment as well, as individuals progress from requiring more significant collaboration with a therapist in early stages, to achieving more independent levels of engagement as skills strengthen. The degree to which therapist involvement is necessary and beneficial, with consideration for the individual needs of the patient, remains an important area for future investigation.

A further consideration is the selection of group-based versus individual treatment. Cognitive and functional improvements in MDD have been derived from cognitive treatments utilising individual as well as group approaches, although the latter has been favoured because of generating an environment for the patient wherein working with others experiencing the same problems (i.e. cognitive difficulties) and shared goals (such as learning and self-improvement) tends to be a motivational factor.<sup>11</sup> In addition to therapeutic advantages, although the evidence on cost-effectiveness of individual versus group psychotherapy remains mixed, there is support for group intervention for depression being an economical alternative to individual treatment.<sup>31,32</sup>

#### Dose and duration of cognitive treatment interventions

There are no published comparative 'dosing' studies of cognitive treatments in MDD, nor has duration of training been considered in analyses. However, effective programmes with participants with MDD have entailed a wide range of sessions, from 6 to 64.<sup>33</sup> In the schizophrenia literature, groups receiving on average 7 sessions have been found to have similar effects to those receiving up to 33 sessions.<sup>34</sup> It has been considered that perhaps individuals with mood disorders might only need short durations of treatment on the basis of more subtle cognitive deficits relative to schizophrenia.

In an interesting study on self-determined treatment intensity, Choi & Medalia<sup>35</sup> allowed patients with severe mental illness

(44% of the participants had a mood disorder) to complete a cognitive remediation programme at their own accord, but they were encouraged to attend sessions twice a week. Authors defined 26 sessions within 4 months as high intensity, whereas taking longer than 4 months to complete 26 sessions was defined as low intensity. High-intensity treatment was associated with greater improvement post-treatment on a measure of sustained attention and clerical accuracy than the improvement for those who received low-intensity treatment. Interestingly, there was no relationship between treatment intensity and behaviour change on a functional measure of work behaviour, suggesting changes in behaviour was not a function of treatment intensity. Thus, higher treatment intensity was associated with greater cognitive improvement (large effect, effect size 0.9), but not functional change.

Recommendations on dose and duration of cognitive interventions specific to MDD are not currently available. In bipolar disorder, there is a general recommendation for neurocognitive psychological interventions to be administered for 10–21 weeks, with assessments of cognitive function at baseline and immediately after treatment, with follow-up 3–6 months later.<sup>1</sup> Meta-analysis of cognitive remediation interventions in schizophrenia<sup>12</sup> has reported a mean intensity of 2 h per week, which remains a common regime in cognitive remediation trials.<sup>13,36</sup>

### Choice of specific cognitive exercises

The following section refers specifically to the repetitive cognitive exercise component of cognitive treatments. Several commercially available packages have computerised tasks that will provide repeated practice on particular cognitive skills.

#### Task selection

Choice of exercises to be practised as part of cognitive treatment trials is important to consider for a number of reasons. First, to ensure improved performance on cognitive measures at treatment end is not simply the effect of familiarity (for example, a practice effect), exercises practised as part of cognitive treatment trials should be different to the tasks included in cognitive testing batteries (see also the Primary outcome section).

Second, in studies that involve comprehensive cognitive assessment prior to commencement of the cognitive intervention, there is the option of selecting specific computerised cognitive training exercises based on the patients' cognitive profile of strengths and weaknesses. A tailored approach is easier to achieve if the cognitive intervention is being conducted individually, rather than in a group-based format. In addition, patients may be more motivated to engage in a cognitive intervention that is specifically designed for their cognitive needs.

#### Level of difficulty and feedback on performance

Two important issues in considering what specific computerised exercises to include in a cognitive treatment are (a) whether direct and immediate feedback is given during performance of the task, and (b) what the optimal level of difficulty should be. The two issues are related, since feedback may negatively influence performance, thereby making the exercise more difficult. Feedback may be an immediate part of the exercise and may be unavoidable for tasks where responses must be correct to proceed to the next response. Alternatively, feedback can be given after completion of a block of the task in the form of a score or percentage correct.

There is some evidence regarding what may be an appropriate level of difficulty for computerised cognitive exercises in MDD, however, this is very preliminary. First, theoretically, producing a low level of frustration may be necessary to engage the prefrontal cortex in the face of amygdala activation, hence, exercises should

not operate at too high a success rate. Second, if success rate is too high, lack of stimulation may be demotivating. Third, previous research indicates that patients who are depressed tend to respond to immediate feedback of failure on cognitive tests in a 'catastrophic' manner,<sup>37</sup> or alternatively, that patients who are depressed may fail to improve performance following an error.<sup>38</sup> These findings suggest that immediate feedback of performance may be problematic in a cognitive treatment trial.

In terms of task difficulty, Holshausen et al<sup>39</sup> asked patients with MDD to self-adjust exercise parameters so that their average accuracy levels approximated 80%. Some set their parameters so that their performance was substantially greater than 80% accuracy. Others had a very dynamic adjustment, giving them a large range but average accuracy around 85%. Therefore, it seems that patients naturally adjust to have a success rate of slightly above 80%. An important point is that the optimal success rate may vary depending on the mood state of patients and it may be appropriate to have a lower success rate as patients become more euthymic.

Overall, maintaining the success rate at approximately 85% may avoid a catastrophic response to perceived failure (or lack of a motivating effect of failure), may facilitate a feeling of success, and may allow relatively positive feedback to be given by the therapist or computer program. However, this may need to be altered as treatment progresses. An important question as we move forward is to determine the degree to which self-paced versus automated parameter adjustment affects progress in therapy. The advantage of the former, even if the range of difficulty is high, stems from the argument that autonomy is a critical feature for cognitive mastery in cognitive interventions.<sup>11</sup>

### Home practice

Home practice of cognitive training exercises is commonly integrated into cognitive treatments. As an important element of the treatment, home practice affords participants the opportunity for daily training and regular dosage of cognitive activation. However, impairment in motivation is a core feature in MDD, which has an impact on ability to engage in and benefit from treatment. Research suggests a high degree of variability in engagement in, and completion of, home practice. For example, in a randomised controlled trials for treatment-resistant MDD,<sup>40</sup> where homework was prescribed at a dose of 2800 min (two sessions of 20 min per day for 10 weeks), completed practice ranged from 33 to 3365 min. Engagement in home practice was related to treatment success, as cognitive improvements were moderately correlated with the amount of homework completed ( $r = 0.47$ ,  $P = 0.02$ ).<sup>40</sup>

#### Monitoring

As with other psychotherapies, review of home practice completion at the beginning of sessions is advised. Most computer training programs afford the opportunity for therapists to monitor the extent to which participants engage in home practice outside of sessions. Review of home practice can be easily integrated into goal-setting and progress discussions throughout the treatment programme.

In addition to objective review of home practice completed via logging into participants' accounts, motivation has been indexed using session attendance,<sup>35,41</sup> or quantification of effort or engagement based upon the number of tasks completed versus the number attempted, relative to the total number of tasks required for completion of the programme.<sup>42</sup> Meusel (2011) reported that engagement and depressive symptom severity predicted magnitude of treatment response, but neither medication load nor degree of baseline cognitive impairment did.<sup>42</sup> For trials with a more independent framework of training, to monitor adherence, patients may be connected with via a phone call. Preiss and colleagues<sup>43</sup> achieved

treatment completion of 52% of their sample of long-term outpatients with unipolar or bipolar disorder, using only monitoring phone calls every 2 weeks.

### Improving adherence

Cognitive difficulties in domains such as memory, attention and executive functioning can affect patient comprehension of treatment instructions, thereby contributing to poor treatment adherence in mood disorders.<sup>44,45</sup> Thus, the therapist should consider adapting the form of instructions to suit the patient: for example, supplementing verbal instruction with visuals, and frequent check-in to provide opportunities to ask questions and assess comprehension. Further, deficits in motivation and effort are integral to cognitive performance in mood disorders,<sup>46</sup> and warrant consideration for their influence on treatment adherence. The ability to put skills into action in the community is often restricted by anhedonia and low motivation,<sup>47</sup> thus, symptoms restricting motivation or confidence to engage in cognitively complex tasks may limit engagement in home practice as well as generalisation of improvements to functioning.

Although poorly studied in MDD, adaptation of treatment in light of motivation deficits has been explored with patients across the schizophrenia spectrum. Attempting to promote motivation by carefully changing the format of learning materials (for example personalising learning materials to increase value, increasing individuals' control over the learning process via opportunity to make choices<sup>48</sup>) or by using motivational interviewing techniques<sup>49</sup> has resulted in increased internal motivation and self-competency, and higher attendance rates of training sessions in psychosis. Thus, integrating intrinsically motivating techniques into cognitive interventions has the potential to promote improved outcomes and motivation to learn for individuals afflicted by conditions that negatively affect motivation.

Common cognitive distortions of people with MDD can influence engagement. For example, black and white thinking (for example 'If I can't do it perfectly, I'm a failure') can limit one's engagement and willingness to participate. Or, participants might become discouraged during initial introduction to cognitively complex tasks, which may provide opportunities to activate negative attributions about oneself.<sup>50</sup> Bowie et al<sup>47</sup> have advised integration of cognitive restructuring from cognitive-behavioural therapy as an important element for improving adherence and retention in treatment.

Finally, increasing behavioural activation within sessions leads to greater treatment retention. When training is integrated with skills training and real-world activity, as well as a more active role of therapists to assist with transfer of strategies to daily activities, significantly more individuals are retained in treatment.<sup>25</sup> Further, continually anchoring home practice in goals set at the onset provides individualised relevance of the treatment throughout, which may enhance adherence.

### Control therapies

Current practice in clinical trials favours the use of 'active' over 'passive' controls (for example a waitlist), since active controls can account for non-specific therapist-related effects. Many control conditions for cognitive treatments rely on some alternative form of sessions controlling for computer skill training and social milieu.<sup>51</sup> Porter et al<sup>50</sup> recommend that ideally the comparison therapy should be of equivalent total time and distribution of sessions, with the same face-to-face versus homework-based practice.

A critical issue facing cognitive interventions is controlling for expectancy and motivation.<sup>33,52</sup> Motter et al<sup>33</sup> advise that one way to mitigate differential performance between the training and control group is to incorporate active control protocols in which

participants also take part in a task that is comparably engaging and consistent in duration and frequency with the active condition.

A further important issue is that of 'therapy leakage'. Therapists and patients in a control treatment may become aware of some of the content of the cognitive treatment and seek to emulate this, possibly using freely available online packages. The degree to which this occurs should be limited and recorded if possible.

### Primary outcome

An important question is how to best track outcomes of cognitive treatment trials. To determine whether the treatment adequately exerts pro-cognitive effects, objective cognitive function should be included as a primary outcome measure. The majority of studies implement multiple cognitive outcomes when investigating pre- to post-treatment change. An alternative strategy is to operationalise treatment success by the number of tests that show a 'clinically relevant' degree of improvement, such as an increase of 1 s.d. or more on at least two of six cognitive tests.<sup>3,53</sup>

The absence of an *a priori* hierarchy between cognitive measures in the majority of randomised controlled trials is a methodological challenge in mood disorders.<sup>3</sup> The Consolidated Standards of Reporting Trials Statement 2010<sup>54</sup> recommends only one primary outcome, although there may be more secondary outcomes. Within schizophrenia research, there is consensus on evaluating treatment effects on cognitive function using the MATRICS Consensus Cognitive Battery (MCCB) with the primary outcome being a global MCCB composite score. Similarly, the recommended procedure for deriving a common metric for cognitive function in bipolar disorder is to calculate the composite score of the tests.<sup>1</sup>

Although most cognitive treatment trials evidence improved cognitive function, a crucial goal of intervention is to promote functional recovery. It is thus advised that researchers use a combination of proximate (i.e. cognitive function, symptoms) and distal (i.e. functional competence and real-world functioning) measures to distinguish effects of cognitive improvement on other aspects of the clinical picture. Further, real-world variables have greater ecological validity and more closely address functional goals of the patient.<sup>41</sup> In determining whether cognitive treatment improves cognitive function, it is important to use cognitive assessment tasks that are not directly related to training tasks,<sup>50</sup> as this allows for delineating changes in performance because of real cognitive improvement or mere expertise on the training task.<sup>41</sup> Additionally, use of subjective cognitive measures can afford the opportunity to measure experienced cognitive improvement.

With regards to durability, when included in cognitive treatment research, durability is typically assessed within 2–3 months following the completion of treatment in study participants with MDD.<sup>55,56</sup> Recently published methodological recommendations for cognition trials in bipolar disorder have suggested administration of follow-up assessment within the 3–6 months post-treatment.<sup>1</sup>

### General methodological issues

#### Power

Power, of course, depends critically on the primary outcome measure. If a composite cognitive score is used, there is no generally agreed 'minimally clinically important difference' on which to base power calculations. It would be helpful to have some discussion and possibly consensus in the literature regarding this. One way of calculating such a metric would be to relate cognitive function to general functioning to determine a cognitive change that would usually result in significant improvement in general functioning. However, measuring general functioning is difficult and it could be argued that if this procedure is used then a functional outcome

should be the primary outcome measure. An alternative power calculation could be based on the percentage of patients who move from impaired to unimpaired based on a predetermined definition of impairment. Studies have also used binary, service-based measures such as readmission rates to conduct power calculations.<sup>57</sup>

#### Nocebo effect

Depending on the control treatment, patients are unlikely to be masked to allocation in cognitive treatment trials. Those who are allocated to the control treatment, particularly if they perceive that they have cognitive problems, may feel disappointed or demotivated and are unlikely to experience the usual placebo effect of being in clinical trials. This may affect mood symptoms and by virtue of reduced engagement in testing at follow-up may confer poorer cognitive performance. Of note, a recent analysis in clinical trials has suggested minimal effect of unmasking. This is reassuring considering the difficulties of masking trials of psychological treatments.<sup>58</sup>

#### Neuroimaging findings in cognitive treatment trials

Research examining the neurobiological effects of cognitive remediation in schizophrenia have tended to show a beneficial effect on brain structure and function. A recent meta-analysis of 19 studies involving 455 adult patients with schizophrenia showed increased activation in prefrontal, occipital and anterior cingulate regions during working memory and executive tasks, as well as improved functional connectivity, in those who had received cognitive remediation ( $n = 271$ ).<sup>59</sup>

Much less neuroimaging research has been conducted in cognitive remediation trials for mood disorders, and specifically MDD, but it would be useful to confirm expected changes in brain functioning, particularly in activation paradigms. Siegle et al showed that a brief cognitive activation treatment involving six sessions of attention control training and the Paced Auditory Serial Addition Task over 2 weeks reduced disruptions in amygdala activity on an emotion processing task and the dorsolateral prefrontal cortex on a cognitive task in patients with unipolar depression ( $n = 6$ ).<sup>4</sup> In a more remediative paradigm, Meusel et al found brain changes detectable on functional magnetic resonance imaging (increased lateral and medial prefrontal, superior temporal, and lateral parietal regions during a working memory task, and increased activation in bilateral hippocampus during a recollection task) in their participants with bipolar disorder with euthymic mood following a 10-week cognitive remediation intervention.<sup>60</sup> However, improved performance on cognitive tests did not correlate directly with changes in functional activation.

This review has provided an in-depth discussion of current approaches in cognitive treatment trials in MDD. There are several methodological issues to consider during the development of cognitive treatment trials, and discussion of these within this review has at times drawn from research in the broader mood disorder and psychosis literature, where relevant. Limited research exists specifically pertaining to cognitive interventions in MDD.

#### Future research

Future research in this area is crucial in order to (a) provide clearer recommendations for clinicians delivering treatment, and (b) develop evidence-based guidelines regarding methodology of cognitive treatment trials for researchers.

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K.M.D., R.J.P. and C.R.B. developed the initial outline of this paper, and all authors were involved in the preparation of the manuscript (each contributed content to specific sections) and editing subsequent revisions. All authors were involved in final approval of the paper.

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K.M.D., C.R.B., M.M. and R.J.P. use software provided free-of-charge by Scientific Brain Training Pro for cognitive remediation trials. R.J.P. has received support for travel to educational meetings from Servier and Lundbeck. C.R.B. has grant support from Lundbeck, Takeda and Pfizer and has received consulting fees from Boehringer Ingelheim, Pfizer and Lundbeck.

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