Cognitive dysfunction in major depressive disorder

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Purpose of review
The principal aim of this review is to highlight recent advances in our understanding of cognitive dysfunction in major depressive disorder (MDD). We review new assessment and treatment approaches, in which cognition and associated psychosocial dysfunction are considered primary outcomes.

Recent findings
Current work suggests that cognitive dysfunction reduces occupational productivity, and interferes broadly with domains of day-to-day and social functioning. These findings imply that cognitive dysfunction interacts with emotional and social factors relevant to MDD. Recent advances in screening instruments enable standardized detection of cognitive symptoms in MDD. Clinical trials suggest that cognitive symptoms are suitable targets and primary outcomes of psychological and pharmacological treatments.

Summary
A growing interest in cognitive dysfunction in MDD has improved our ability to assess and treat MDD. Future research will be strengthened by the use of consistent terminology, standardized cognitive screening, and treatments that target cognitive dysfunction in MDD. Integration of emotional and social treatment strategies may further advance clinical efficacy.

Keywords
cognition, cognitive remediation, cognitive training, executive functioning, major depressive disorder, screening, treatment

INTRODUCTION

Major depressive disorder (MDD) is characterized by impaired affect, cognitive dysfunction, and significant psychosocial impairment that persists from weeks to years [1]. Cognitive symptoms are pervasive, affecting functioning in a number of domains including reduced executive functioning, attention, memory, learning, psychomotor speed, and verbal processing [2,3▪▪,4]. Recent evidence suggests that cognitive dysfunction persists following symptomatic remission [4,5], highlighting the need to treat cognition separately from mood symptoms. Residual cognitive deficits may contribute to ongoing occupational and social dysfunction [5–8] and promote suicide ideation [9]. In addition, retention of cognitive impairment may interact with existing emotional and social vulnerability, increasing the risk of recurrent depressive episodes [10,11].

We review the extent of domain-specific cognitive deficits observed in MDD. It is suggested that cognitive dysfunction is broad and negatively affects a number of psychosocial domains. Recent advances in screening instruments are discussed, which suggest cognitive dysfunction negatively affects psychosocial functioning independently of mood symptoms. The efficacy of current psychological and pharmacological treatments for cognition is reviewed, arriving at a consensus of the most successful strategies employed thus far. The review is concluded with a discussion of 'hot' and 'cold' cognitive functioning, and the integration of social cognition and emotion processing in cognitive treatment [12].

DOMAINS OF COGNITIVE IMPAIRMENT IN MAJOR DEPRESSIVE DISORDER

Current reviews suggest broad cognitive deficits in MDD, which are associated with impaired daily and psychosocial functioning [3▪▪,6]. However, there is no firm consensus regarding which domains of cognition are selectively affected by depression [13], and hence which domains should be primary treatment targets. This uncertainty is caused in part

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KEY POINTS

- Cognitive dysfunction in MDD is broad and is related with psychosocial functioning and depression recovery.
- Recently developed screening tools enable identification of subjective and objective cognition symptoms in MDD.
- Cognitive remediation, cognitive training, and pharmacological treatment facilitate cognitive improvements in MDD.
- Integration of social cognition and emotion processing in cognitive treatment may advance clinical efficacy in MDD.

by varied patterns of comorbidity and individual differences which affect cognitive functioning. However, ambiguous terminology and conceptual understanding of cognitive domains also contribute to uncertainty regarding cognitive deficits – an issue identified by authors who face difficulty in comparing cognitive functioning between studies [14▪▪].

Recent literature has identified impairment across several executive domains, including set shifting, inhibition, working memory, and verbal processing [3▪▪,10,13,14▪▪]. Models of cognition and MDD underscore the vital importance of executive functioning in daily life and psychosocial abilities [4,15▪], suggesting that executive impairment may be a primary barrier to functional recovery in individuals with MDD. Although the domain-specific nature of executive impairment remains to be drawn out, current work supports the notion that executive remediation should be a primary target of cognitive treatment. Verbal processing, attention, learning, and memory also appear to be impaired by MDD [3▪▪]. Given the importance of verbal memory and attention in occupational and social settings, it stands to reason that impairment in these domains may disrupt psychosocial functioning [10]. Recent reports of impaired visuospatial processing in MDD are not consistent [13,16–18]. However, patients with psychotic symptoms typically demonstrate lower visuospatial skills than depressed patients without psychoses [16,17], highlighting the need to consider comorbid illness and personalized treatment. The importance of visuospatial cognition in functional recovery may depend on the primacy of visuospatial skills in individuals' occupational and everyday activities; however, this notion is yet to be empirically tested. Self-reported cognitive dysfunction is widely reported; however, there are inconsistent accounts as to whether subjective evaluations of cognition correlate with objective tests [2,19,20], or with real-world functioning [21].

Although cognitive dysfunction is detrimental in and of itself, there is growing evidence that cognitive issues also cause psychosocial impairment in individuals with MDD. In particular, recent work shows a relationship between self-reported cognitive dysfunction and loss of occupational productivity, impaired social and leisure activities, and reduced daily functioning [10,22,23▪]. Psychosocial and cognitive issues result in significant disability in the daily lives of depressed individuals [22], and often persist despite remission of mood symptoms [24]. Residual psychosocial dysfunction promotes recurrent depressive episodes [4], and hence prolongs the longitudinal impact of MDD [7]. The extent and magnitude of disability caused by psychosocial issues suggests that functional recovery from MDD is reliant upon remediation underlying cognitive symptoms [7,23▪]. It follows that cognitive symptoms should be considered a clinically important treatment target, as improving affect alone is not sufficient to achieving functional or lasting recovery. This notion is currently under investigation by a clinical trial, evaluating the clinical efficacy of cognitive treatment for psychosocial dysfunction in MDD [12]. Taken together, current work suggests that cognitive dysfunction mediates psychosocial and day-to-day impairment in depressed individuals, and that measurement of cognitive impairment should be included in clinical assessment of MDD [20,25].

SCREENING FOR COGNITIVE DYSFUNCTION IN MAJOR DEPRESSIVE DISORDER

Valid and reliable screening tools are crucial to the identification and treatment of cognitive dysfunction in MDD [2,23▪,26]. Existing clinical interviews for MDD (e.g., the Hamilton Depression Scale, the Montgomery-Åsberg Depression Rating Scale) incorporate subjective reports of cognitive functioning, but do not employ objective measures. Subjective cognition is coloured by emotional state [27] and may hence be affected by the severity of mood symptoms to a greater extent than objective cognition. Although subjective cognition is informative of *perceived* dysfunction [2], it may not reflect objective cognitive ability [15▪]. Recent work suggests that objective dysfunction negatively affects organization and occupational and social functioning [10,19], and may contribute to the maintenance and recurrence of MDD. As such there is a clear need for objective screening tools to be incorporated in clinical and research settings.

Face validity and tolerability are important to consider with regards to screening for cognitive

dysfunction in MDD. Specifically, it should be clear to patients that cognitive screening tools are not a covert attempt to test for dementia-related cognitive decline [18]. This is an issue particularly when screening for depression in the elderly, who may fear a dementia prognosis, or assume their clinician is not listening to concerns regarding depressed mood. Indeed, some clinicians maintain the erroneous view that cognitive issues are exclusive to elderly patients [17]; an assumption incongruent with the prevailing psychiatric literature. Patients' understanding of screening tools is imperative to maintaining accurate subjective reports, and to upholding beneficial client–clinician relationships. Clinicians should strive to dismantle the stigma surrounding cognitive screening, while employing screening tools intended for MDD [e.g., Thinc, Screen for Cognitive Impairments in Psychiatry-D (SCIP-D), Cognitive Complains in Bipolar Disorder Rating Assessment (COBRA)] rather than dementia or age-related decline (e.g., the Montreal Cognitive Assessment).

Screening instruments should be short, easy to administer, and use a battery of domain-specific tests [15▪,16]. These criteria are met by the recently developed THINC-it tool (http://thinc.progress.im/en/content/thinc-it-tool), which was designed to address the need for screening cognitive dysfunction in MDD [23▪]. Four well validated objective tests of cognition are included: 1-back (*symbol check*), digit symbol substitution (*codebreaker*), trail making part-B (*trails*), and choice reaction time (*spotter*). These tasks test working memory, visuospatial coordination, set shifting and psychomotor speed. Subjective cognition is evaluated with a five-item Perceived Deficits Questionnaire (PDQ-5). Completing all THINC-it components takes 10–20 min, and task instructions are incorporated such that administration responsibilities are minimal [15▪]. A validation study of the THINC-it tool [15▪] demonstrated that subjective and objective cognitive function were impaired in depressed patients relative to healthy controls. The magnitude of this impairment was consistent with lengthier batteries of cognitive functioning (e.g., CogState, PDQ-20), supporting concurrent validity of the THINC-it tool. In addition, subjective cognitive functioning measured by the THINC-it tool was associated with psychosocial functioning independently of depression symptom severity. These findings suggest that objective and subjective cognition measured by the THINC-it tool are valuable measures of functioning and support the use of the THINC-it tool in clinical and research settings [10].

The SCIP and the COBRA have recently been tested for use in MDD samples [2]. The SCIP includes five objective tests: immediate and delayed digit span, verbal fluency test with letters S and D, digit–letter substitution, and trail making part A. The COBRA is a 16-item questionnaire initially designed to evaluate cognitive concerns in Bipolar Disorder. Taken together, these tests take 20–30 min. As with the THINC-it tool, subjective cognition (i.e., COBRA responses) and objective functioning (i.e., SCIP performance) were not related, supporting their interpretation as discrete measures. Subjective cognition reported in the COBRA was to be related to psychosocial functioning; however, this effect was not independent of depression symptom severity. Conversely, performance in executive measures of the SCIP (i.e., verbal fluency, digit span) were independently related to psychosocial dysfunction. Test characteristics of the SCIP-D, COBRA, and THINC-it tool are presented in Table 1.

Table 1. Properties of the THINC-it, SCIP-D, and COBRA screening tools

Cognitive Testing Instrument/Test characteristics	THINC-it	SCIP-D	COBRA
Screening tool	yes	yes	yes
Validated in Depression	yes	yes	yes
Objective tests	yes	yes	no
Subjective tests	yes	no	yes
Level of required instructions by third person	low	high	low
Self-instructed testing	yes	no	yes
Administration time	15–20 minutes	15–20 minutes	3–5 minutes

Objective cognition in the SCIP relies to a greater extent on verbal processing in comparison with the THINC-it tool, evident in the use of two verbal digit [15▪] span tests, and a verbal fluency test in the SCIP battery. In contrast, the THINC-it tool relies to a greater extent on visuospatial processing, evident in the choice reaction time and 1-back tasks. In addition, the THINC-it tool may rely to a greater extent on set shifting and updating, as these executive functions are required for trail making part B [3▪▪] and the 1-back task [28]. Further research is needed to determine whether verbal (SCIP) or visuospatial/executive functions (THINC-it) are optimal screening measures for cognitive dysfunction in MDD. Current findings support the use of both the THINC-it tool and the SCIP/COBRA batteries for cognitive screening, as both report cognitive measures related to psychosocial domains.

COGNITIVE REMEDIATION, COGNITIVE TRAINING, AND PHARMACOLOGICAL TREATMENTS

Although past reviews of clinical efficacy in the treatment of depression have typically focussed on mood symptoms [29], more recent work increasingly addresses cognitive dysfunction as a primary clinical outcome. Improvements in cognitive functioning are often compared following Cognitive Remediation and antidepressant treatment [14▪▪,19]. Cognitive remediation involves repeated training tasks targeting specific domains of functioning (e.g., verbal memory, psychomotor speed), generally completed on a computer. Cognitive training programmes follow the rationale that repeated stimulation of neural networks involved in cognitive tasks improves neuroplasticity and enhances cognitive ability. These benefits are expected to transfer to psychosocial domains [3▪▪], a process facilitated by discussion of the everyday application of cognitive skills with a clinician. Cognitive training is a relatively new approach to the treatment of MDD [3▪▪], having typically been employed in the treatment of anxiety disorders [30].

Motter *et al.* [3▪▪] conducted a meta-analysis of cognitive and psychosocial outcomes following computerized cognitive remediation programmes. The authors found that cognitive remediation improved attention and working memory, as measured by the Trail Making task, Part A, and *n*-back task, respectively. Clinical benefits also arose in domains of daily functioning (e.g., social skills, work ability) and global functioning (e.g., Wechsler Adult Intelligence Scale, verbal intelligence quotient). Taken together, these findings support the clinical efficacy of cognitive remediation with regards to promoting improved cognitive function in depressed individuals, and transferring these improvements to psychosocial domains. It is noteworthy that verbal memory (i.e., Hopkins Verbal Learning Test) and executive functioning (e.g., Trail Making Test Part B, Stroop Task) were unaffected by cognitive remediation. It is possible that the problems with standardization of 'executive' tasks have interfered with comparing results of executive training, as studies use different training tasks and outcome measures. These findings reinforce the need for standardized terminology and measurement tools to clarify the effect of cognitive remediation on executive functioning, ideally discriminating its separate components (e.g., set shifting, inhibition).

Although pharmacological treatments including selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors are widely used to promote remission of depression symptoms, their effects on cognition and functional recovery are not well established. The lack of consensus is in part caused by cognition receiving attention primarily as a potential negative side effect [6,16,31], as opposed to a beneficial clinical outcome. Procognitive effects of antidepressants therefore present a valuable opportunity for current research. Recent reviews of antidepressants suggest that SSRIs produce either a neutral or positive effect on cognition [16,17]. The SSRIs Sertraline and Escitalopram appear beneficial in domains of psychomotor speed, cognitive flexibility, memory and executive functioning (i.e., inhibition, attention) [17]. However, these effects may not extend to elderly populations, whose cognitive functioning is less affected SSRI treatment [14▪▪,17]. The recently developed compound Vortioxetine has demonstrated positive effects in domains of memory, psychomotor speed, attention, learning, and verbal working memory [14▪▪,16,17], providing evidence for a broad improvement in cognitive skills [32] even in studies in which cognitive function was a primary outcome. In addition, cognitive gains following Vortioxetine treatment in MDD show related better day-to-day functioning [17], possibly due to the beneficial effect on broad cognitive improvement. Although Duloxetine also shows procognitive effects, these occur across fewer domains than Vortioxetine [14▪▪]. A recent meta-network analysis [33] that directly compared the effects of a variety of antidepressants on the cognitive measure of the Digit Symbol Substitution test (DSST), found a more beneficial effect of Vortioxetine on the DSST when compared with any other antidepressant. The anaesthetic Ketamine is currently undergoing testing as a new pharmacological treatment option for MDD [31,34]; however, initial findings indicate that Ketamine does not affect cognitive functioning [31]. Recent findings suggest that psychostimulants (e.g., dexamphetamine) promote rapid, short-term relief from depression symptoms [35]. However, there is a paucity of evidence for their long-term clinical efficacy in depression and on cognitive symptoms in MDD, underscoring the need for clinical trials of psychostimulants.

'HOT' AND 'COLD' COGNITION: INTERACTIONS AND IMPLICATIONS

Current clinical and cognitive literature often use the terminology of 'hot' and 'cold' cognition to refer to cognitive functions which are either influenced by emotional state (i.e., 'hot'), or independent of emotional state (i.e., 'cold'). These definitions of cognitive functioning are useful when discussing psychological interventions, such as cognitive behavioural therapy, which aim to address maladaptive 'hot' cognition

(e.g., negative attentional bias) as opposed to 'cold' cognition. Although useful, these definitions may promote a dichotomous view of cognitive science in which 'hot' and 'cold' cognition are distinct and separable entities. Current work is at odds with this notion [7], as neuroimaging studies have identified overlapping neural networks for cognitive and emotional processes [36,37], implying a shared effect on behaviour and functioning. Further evidence for the integration of 'hot' and 'cold' cognitive functioning is found in neuropsychological tests, the results of which are influenced by emotional state [38]. In social contexts, the maintenance of 'cold' functions including attention and verbal processing is highly reliant on emotional state, and perceived social repercussions, highlighting the intrinsic link between cognition and social/emotional factors [39]. Future clinical work may be improved by integrating models of social cognition and emotion processing with cognitive functioning [12]. Specifically, cognitive remediation programmes for MDD may benefit from considering concurrent social cognitive and emotion processing impairment as novel treatment targets in conjunction with the remediation of cognitive symptoms [12,16,38]. Mutual interaction between these factors may prevent or attenuate the clinical efficacy of current cognitive remediation, in which 'cold' cognition is emphasized above social cognition and emotion processing. Integrating treatment across these domains (i.e., cognition, emotion processing, social cognition) may improve functional and day-to-day outcomes relative to existing cognitive remediation strategies.

CONCLUSION

In summary, this review suggests that cognitive dysfunction in MDD is pervasive across multiple domains and is reflected in both subjective and objective measures. Current literature suggests that cognitive impairment mediates psychosocial and everyday dysfunction and should hence be included in assessment and treatment of MDD. The use of validated screening tools (e.g., THINC-it tool and SCIP/COBRA) and refined definitions of cognitive domains will facilitate our understanding of cognitive dysfunction and improve evaluation of clinical efficacy. Recent evidence supports cognitive training and remediation, and select pharmacological treatments (e.g., Vortioxetine), in the treatment of cognitive dysfunction and associated psychosocial issues. Future cognitive training and remediation programmes may be improved by integrating social cognition and emotion processing into such treatment approaches to MDD, as these domains are closely tied to cognitive functioning and may interact in patient recovery from MDD [11,16]. Future work should evaluate the efficacy of psychological and pharmacological combined and personalized treatment approaches, with cognition and psychosocial functioning considered primary outcomes [12].

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Conflicts of interest

B.T.B. receives speaker/consultation fees from: AstraZeneca, Lundbeck, Pfizer, Takeda, Servier, Bristol Myers Squibb, Otsuka, and Janssen-Cilag, and played a role in the development of the THINC-it tool. M.K. has no conflicts of interest to declare.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. American Psychological Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, DC: American Psychiatric Pub; 2013.
2. Ott CV, Bjertrup AJ, Jensen JH, *et al.* Screening for cognitive dysfunction in unipolar depression: validation and evaluation of objective and subjective tools. J Affect Disord 2016; 190:607–615.
3. ■■ Motter JN, Pimontel MA, Rindskopf D, *et al.* Computerized cognitive training and functional recovery in major depressive disorder: a meta-analysis. J Affect Disord 2016; 189:184–191.

The article provides a comprehensive meta-analysis of the clinical efficacy of computerized cognitive training strategies for the treatment of major depressive disorder (MDD).

4. Baune BT, Air T. Clinical, functional, and biological correlates of cognitive dimensions in major depressive disorder – rationale, design, and characteristics of the cognitive function and mood study (CoFaM-Study). Front Psychiatry 2016; 7:150.
5. Baune BT, Miller R, McAfoose J, *et al.* The role of cognitive impairment in general functioning in major depression. Psychiatry Res 2010; 176:183–189.
6. Clark M, DiBenedetti D, Perez V. Cognitive dysfunction and work productivity in major depressive disorder. Expert Rev Pharmacoecon Outcomes Res 2016; 16:455–463.
7. McIntyre RS, Lee Y. Cognition in major depressive disorder: a 'Systemically Important Functional Index'(SIFI). Curr Opin Psychiatry 2016; 29:48–55.
8. Fried EI, Nesse RM. The impact of individual depressive symptoms on impairment of psychosocial functioning. PLoS One 2014; 9:e90311.
9. Richard-Devantoy S, Ding Y, Lepage M, *et al.* Cognitive inhibition in depression and suicidal behavior: a neuroimaging study. Psychol Med 2016; 46:933–944.
10. Cha DS, Carmona NE, Subramaniapillai M, *et al.* Cognitive impairment as measured by the THINC-integrated tool (THINC-it): Association with psychosocial function in major depressive disorder. J Affect Disord 2017; 222:14–20.
11. Weightman MJ, Air TM, Baune BT. A review of the role of social cognition in major depressive disorder. Front Psychiatry 2014; 5:179.
12. Australian New Zealand Clinical Trials Registry: Sydney (NSW); NHMRC Clinical Trials Centre; University of Sydney (Australia). Cognitive and emotional recovery training for depression (CERT-D). In: 2005 – Identifier ACTRN12617000899347; 2017:; 7; Available from http://www.anzctr.org.au/ACTRN12617000899347.aspx. [Cited 12 September 2017]

13. Davis MT, DellaGioia N, Matuskey D, *et al.* Preliminary evidence concerning the pattern and magnitude of cognitive dysfunction in major depressive disorder using cogstate measures. J Affect Disord 2017; 218:82–85.

14. ■■ Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol 2016; 19:.

The authors present the first meta-analysis of randomised controlled trials, evaluating the clinical efficacy of antidepressants for the treatment of cognitive symptoms in MDD.

15. ■ McIntyre RS, Best MW, Bowie CR, *et al.* The THINC-integrated tool (THINC-it) screening assessment for cognitive dysfunction: validation in patients with major depressive disorder. J Clin Psychiatry 2017; 78:873.

A validation study of the THINC-it tool which indicates strong concurrent and discriminant validity, as well as high reliability, supporting further use of the THINC-it tool to screen for cognitive symptoms in clinical assessment of MDD.

16. MacQueen GM, Memedovich KA. Cognitive dysfunction in major depression and bipolar disorder: assessment and treatment options. Psychiatry Clin Neurosci 2016; 71:18–27.

17. Salagre E, Solé B, Tomioka Y, *et al.* Treatment of neurocognitive symptoms in unipolar depression: a systematic review and future perspectives. J Affect Disord 2017; 221:205–221.

18. Liao W, Zhang X, Shu H, *et al.* The characteristic of cognitive dysfunction in remitted late life depression and amnestic mild cognitive impairment. Psychiatry Res 2017; 251:168–175.

19. Miskowiak K, Ott C, Petersen J, Kessing L. Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field. Eur Neuropsychopharmacol 2016; 26:1845–1867.

20. Potvin S, Charbonneau G, Juster R-P, *et al.* Self-evaluation and objective assessment of cognition in major depression and attention deficit disorder: implications for clinical practice. Compr Psychiatry 2016; 70:53–64.

21. Beblo T, Kater L, Baetge S, *et al.* Memory performance of patients with major depression in an everyday life situation. Psychiatry Res 2017; 248:28–34.

22. IsHak WW, James DM, Mirocha J, *et al.* Patient-reported functioning in major depressive disorder. Ther Adv Chronic Dis 2016; 7:160–169.

23. ■ Baune BT, Malhia GS, Morris G, *et al.* Cognition in depression: can we THINC-it better? J Affect Disord 2017; 225:559–562.

The article draws together the conclusions of several leading researchers and clinicians, suggesting that cognitive symptoms of MDD are closely linked with functional outcomes and that cognitive screening should be included in clinical assessment.

24. Pehrson AL, Leiser SC, Gulinello M, *et al.* Treatment of cognitive dysfunction in major depressive disorder – a review of the preclinical evidence for efficacy of selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors and the multimodal-acting antidepressant vortioxetine. Eur J Pharmacol 2015; 753:19–31.

25. Ott CV, Vinberg M, Kessing LV, Miskowiak KW. The effect of erythropoietin on cognition in affective disorders – associations with baseline deficits and change in subjective cognitive complaints. Eur Neuropsychopharmacol 2016; 26:1264–1273.

26. Hammi EE, Samp J, Rémuzat C, *et al.* Difference of perceptions and evaluation of cognitive dysfunction in major depressive disorder patients across psychiatrists internationally. Ther Adv Psychopharmacol 2014; 4:22–29.

27. Strober LB, Binder A, Nikelshpur OM, *et al.* The perceived deficits questionnaire: perception, deficit, or distress? Int J MS Care 2016; 18:183–190.

28. Morris N, Jones DM. Memory updating in working memory: the role of the central executive. Br J Psychol 1990; 81:111–121.

29. Thase ME, Greenhouse JB, Frank E, *et al.* Treatment of major depression with psychotherapy or psychotherapy–pharmacotherapy combinations. Arch Gen Psychiatry 1997; 54:1009–1015.

30. MacLeod C, Grafton B. Anxiety-linked attentional bias and its modification: illustrating the importance of distinguishing processes and procedures in experimental psychopathology research. Behav Res Ther 2016; 86:68–86.

31. George D, Gálvez V, Martin D, *et al.* Pilot randomized controlled trial of titrated subcutaneous ketamine in older patients with treatment-resistant depression. Am J Geriatr Psychiatry 2017. [Epub ahead of print]

32. Harrison JE, Lophaven S, Olsen CK. Which cognitive domains are improved by treatment with vortioxetine? Int J Neuropsychopharmacol 2016; 19:1–6.

33. Baune BT, Brignone M, Larsen KG. A network meta-analysis comparing effects of various antidepressant classes on the digit symbol substitution test (DSST) as a measure of cognitive dysfunction in patients with major depressive disorder. Int J Neuropsychopharmacol 2017. (In press).

34. Short B, Fong J, Galvez V, *et al.* Side-effects associated with ketamine use in depression: a systematic review. Lancet Psychiatry 2017. [Epub ahead of print]

35. Malhi GS, Byrow Y, Bassett D, *et al.* Stimulants for depression: on the up and up? Aust N Z J Psychiatry 2016; 50:203–207.

36. Shackman AJ, Salomons TV, Slagter HA, *et al.* The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat Rev Neurosci 2011; 12:154–167.

37. Raz G, Touroutoglou A, Wilson-Mendenhall C, *et al.* Functional connectivity dynamics during film viewing reveal common networks for different emotional experiences. Cogn Affect Behav Neurosci 2016; 16:709–723.

38. Bortolato BF, Carvalho A, McIntyre SR. Cognitive dysfunction in major depressive disorder: a state-of-the-art clinical review. CNS Neurol Disord Drug Targets 2014; 13:1804–1818.

39. Sanchez-Moreno J, Martinez-Aran A, Vieta E. Treatment of functional impairment in patients with bipolar disorder. Curr Psychiatry Rep 2017; 19:3.