CNS Spectrums

www.cambridge.org/cns

Perspectives

Cite this article: Petersen CS, and Miskowiak KW. Toward a transdiagnostic neurocircuitry-based biomarker model for pro-cognitive effects: challenges, opportunities, and next steps. *CNS Spectrums* https://doi.org/10.1017/S1092852920000061

Received: 10 October 2019
Accepted: 09 January 2020

Key words:
Cognitive impairment; fMRI; neural underpinnings; dorsal prefrontal cortex; default mode network; neurocircuitry-based biomarker model

Author for correspondence:
*Kamilla W. Miskowiak,
Email: kamilla@miskowiak.dk

Toward a transdiagnostic neurocircuitry-based biomarker model for pro-cognitive effects: challenges, opportunities, and next steps

Cecilia S. Petersen[1,2] and Kamilla W. Miskowiak[1,2]*

[1]Department of Psychology, University of Copenhagen, Copenhagen, Denmark, and [2]CADIC, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Abstract

Cognitive impairment has emerged as a key treatment priority in neuropsychiatric disorders. However, there is a lack of treatments with solid and lasting efficacy on cognition. A neurocircuitry-based biomarker model of pro-cognitive effects is critically needed to select among new candidate treatments. In a recent review of functional magnetic resonance imaging (fMRI) studies in mood disorders, we found that cognitive impairments are consistently accompanied by aberrant (hypo- and hyper-) activity in the dorsal prefrontal cortex (PFC) and the default mode network (DMN), and that activity change in these regions commonly occurs with cognitive improvements. Here, we (i) review the putative model from our recent review article, which explains the discrepant findings regarding the *direction* of aberrant dorsal PFC activity and treatment-related activity change in mood disorders. Inspired by the Research Domain Criteria project, we do this in order to (ii) examine whether a similar pattern of activity change occurs across distinct neuropsychiatric disorders and thereby provides a common biomarker for pro-cognitive effects. Lastly, we (iii) discuss whether dorsal PFC and DMN target engagement is a putative transdiagnostic neurocircuitry-based biomarker model for pro-cognitive effects, and (iv) outline the necessary next steps to address this question.

Cognition as a Transdiagnostic Treatment Target

Cognitive impairment is a core feature of most neuropsychiatric disorders and is closely related to the functional outcome and societal costs of mental illness.[1–3] Indeed, cognitive impairment often persists in asymptomatic phases of the disorders and is a stronger predictor of socio-occupational capacity than psychiatric symptoms, including hallucinations or subsyndromal depressive symptoms.[2,4,5] In Europe alone, reduced work capacity due to psychiatric disorders annually costs an estimated €315 billon, which constitutes 40% of the total expenditures associated with the disorders.[6] Cognitive impairment is also a consistent predictor of poor treatment efficacy of both psychological and pharmacological interventions,[7,8] contributing to reduced chances of recovery and a prolonged illness duration.[1,2] Cognition has therefore emerged as a critical therapeutic target in psychiatric disorders to improve patient recovery and vocational function, thereby reducing societal costs.[1,4] Nevertheless, current treatments lack robust and long-lasting efficacy on cognitive impairments.[1,8]

Challenges and Possible Solutions for Development of Cognition Treatments

Over the past two decades, substantial research efforts have been invested in the discovery of treatments to restore cognition in neuropsychiatric disorders.[1,3] Nevertheless, there are currently no clinically available pharmacological treatments that have had decisive success in achieving this goal.[9–11] This is partially due to the common methodological challenge in the field, concerning a lack of a valid and sensitive neurocircuitry-based biomarker for pro-cognitive effects to aid decision making in drug development strategies (eg, reference 10). Therefore, drug screening typically relies on animal models and if beneficial effects are seen, the compounds are moved directly into costly clinical efficacy (phase 3) trials. However, discovery of pro-cognitive effects of a compound in animal models provides poor prediction of its efficacy in humans.[12]

According to the psycho-biological Research Domain Criteria project (RDoC)[13] initiated by the National Institute of Mental Health, difficulties with identifying biomarkers are not only related to cognition. Instead, they represent a global challenge within the field of psychiatry.[14,15] The challenge originates in a primary focus on broad psychiatric diagnoses that suffer from high *intra-diagnostic* heterogeneity and high *inter-diagnostic* symptom overlap, which complicates the identification of unitary biological correlates.[14] To ensure a better match of *granularity* between psychological and biological measures, RDoC proposes that psychopathology should be studied by

CAMBRIDGE UNIVERSITY PRESS

relating narrowly defined symptoms (that may occur transdiagnostically) to disruptions of brain circuits.[16] Indeed, the most fundamental assumption of RDoC is that psychiatric illnesses should be considered disorders of brain circuits and that normalization of neurocircuitry functioning will therefore alleviate the symptoms.[17,18] In keeping with this view, a promising way to aid treatment development targeting transdiagnostic cognitive impairments, would be to identify key neurocircuitries associated with cognitiveimpairment and -improvement *across* disorders. As a result, target engagement within these neurocircuitries could become a transdiagnostic biomarker model for pro-cognitive effects that could be implemented in small-scale phase 2 trials. This would aid decision making regarding new candidate cognition treatments prior to initiation of large-scale (costly) phase 3 efficacy trials.

Common Neural Correlates for Cognitive Impairments and Improvements Across Mood Disorders

In a recent systematic review of functional magnetic resonance imaging (fMRI) studies of cognitiveimpairment and -improvement across mood disorders, we identified some promising neurocircuitry-based targets for future cognition treatments.[19] Abnormal (hypo- and hyper-) activation of the dorsal prefrontal cortex (PFC) and failure to suppress the default mode network (DMN) were consistently observed across mood disorders and cognitive domains[19] (Figures 1 and 2). This finding is similar to that of a previous review article in depression by Fossati.[20] Furthermore, we found emerging evidence from a few studies that modulation of activity within these networks was related to cognitive improvement[21–24] (for a discussion of the quality of study results, see reference 19; Figures 1 and 2). Inspired by the work of Callicott et al[25] in patients with schizophrenia and the transdiagnostic thinking of RDoC, we suggested that the variable findings regarding the *direction* of aberrant dorsal PFC activity could be explained by differences between task loads and patients' performance levels across studies.[19] Specifically, hypo-activity was commonly observed in patients with *impaired* performance, whereas hyper-activity was associated with *preserved* performance. Accordingly, hypo-activity likely reflects lower *cognitive capacity* (ie, impaired performance), whereas hyper-activity reflects lower *cortical efficiency* (ie, having to recruit more neural resources to maintain normal performance)[19] (Figure 1). Callicott et al[25] suggested that the association between task load and fMRI response follows an inverted U-shaped curve across patients with schizophrenia and healthy controls, but that the curve for patients is shifted in the direction of lower task loads. This implies that patients reach their peak blood-oxygen-level-dependent (BOLD) response and thereby their cognitive capacity at a lower task load than healthy controls, after which activity declines and performance starts to deteriorate.[25] A similar interpretation of discrepant findings regarding PFC activity during cognitive performance in schizophrenia has been presented in a review article by Manoach.[26] In our systematic review, we found evidence for a similar association between the direction of activity abnormalities in dorsal PFC and cognitive performance in patients with mood disorders.[19] However, in our opinion, the association is better explained by bell-shaped (as opposed to inverted U-shaped) load-response curves that are more compatible with the physiology of neural activity measures, and better illustrate the observed hypo- and hyper-activity in patients at different task loads (Figure 1).

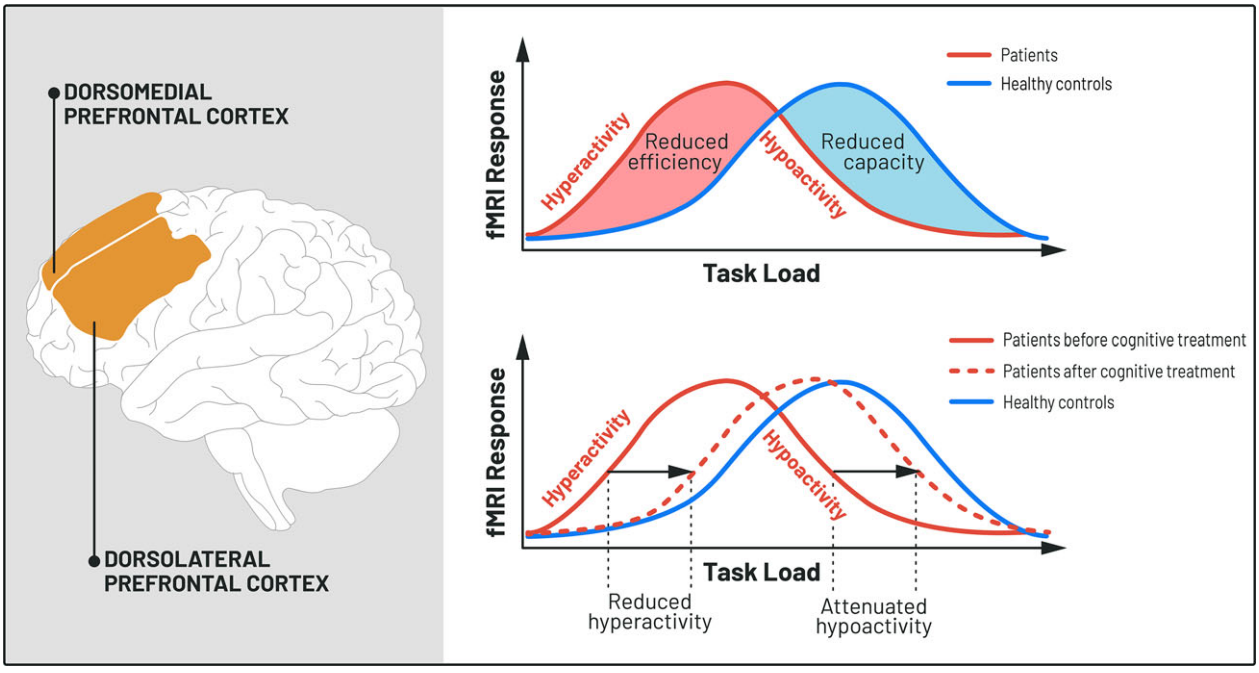

Figure 1. Integrative model to explain the variability in findings regarding the direction of aberrant dorsal prefrontal (PFC) response in patients and treatment-related dorsal PFC activity change. Left: Dorsolateral and dorsomedial PFC regions commonly identified as showing abnormal (hypo- or hyper-) activity in mood disorders. Top right: Hypothesized association between dorsal PFC response in patients and healthy controls at increasing cognitive task loads. The bell-shaped "load-response" curve indicates increase in fMRI response with increasing task load until the task load exceeds people's cognitive capacity after which the activity (and performance levels) declines. The bell-shaped curve for patients lies to the left of the curve for healthy controls, indicating that patients reach their maximum capacity sooner (at lower task loads) than controls. This implicates hyper-activity in patients with preserved performance (reduced efficiency) at low-to-moderate task loads and hypo-activity in patients with poorer performance at moderate-to-high task loads (reduced capacity). Bottom right: Hypothesized rightward shift in the bell-shaped "load-response" curve toward normality, which can explain treatment-related reduction in dorsal PFC hyper-activity in patients who show no cognitive change as well as attenuated dorsal PFC hypo-activity in patients who show cognitive improvements.

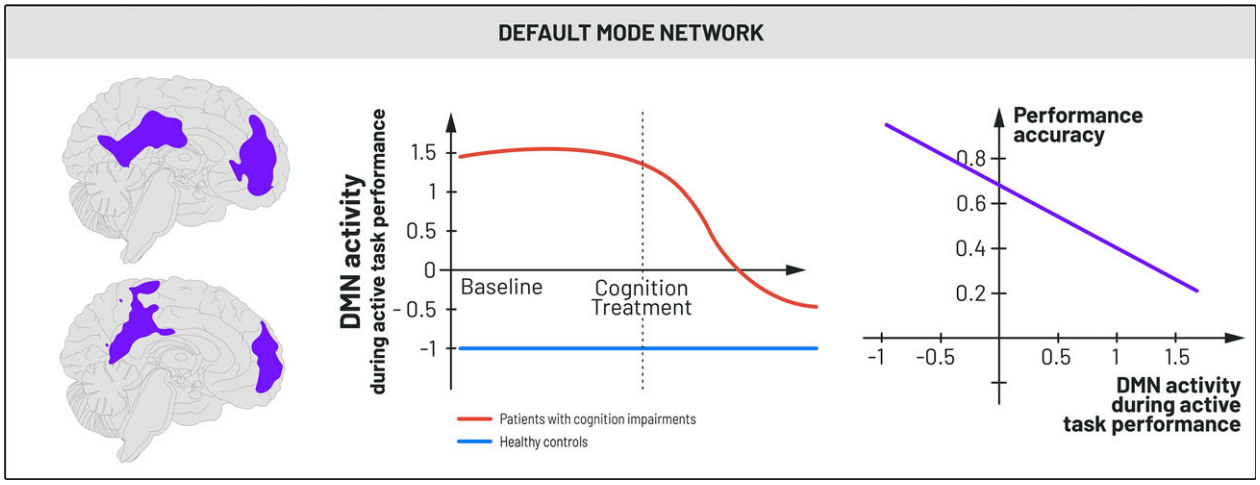

Figure 2. Exaggerated default mode network (DMN) activity in patients, effects of cognition treatment, and association with cognitive performance. Left: DMN regions that consistently show exaggerated activity in patients relative to healthy controls during active task performance. Middle: Illustration of the commonly observed failure to deactivate the DMN during task performance, which is hypothesized to contribute to patients' cognitive impairments, as well of the emerging evidence for treatment-related DMN deactivation. Right: Repeatedly observed negative association between DMN activity during task performance and performance accuracy.

Based on the emerging findings from the intervention studies, we suggest that *cognitive improvement* following distinct treatments targeting cognition is associated with a normalization of aberrant dorsal PFC activity and reduction of hyper-activity in the DMN[21–24] (Figures 1 and 2). Notably, the *direction* of dorsal PFC activity change varied across cognition trials, depending on whether or not patients exhibited an increase in their cognitive performance.[19] According to our model (Figure 1), the apparent discrepancy in the direction of activity change can be explained by a common treatment-related shift in patients' load-response curve in the direction of "normality."[19] Specifically, this shift toward normality is reflected by either (i) a reduction of pretreatment dorsal PFC hyper-activity in patients with no treatment-related performance change (ie, enhanced efficiency) for tasks of medium difficulty levels or (ii) an attenuation of pretreatment hypo-activity in dorsal PFC (ie, increased activity) in patients showing treatment-related cognitive improvement (ie, increased capacity) in more difficult tasks.

Toward a Transdiagnostic Biomarker Model for Pro-Cognitive Effects

Based on the above key findings of our review[19] and inspired by RDoC, we suggest that treatment-related modulation of neural activity in dorsal PFC and DMN is a putative biomarker model for pro-cognitive effects that may be *more* broadly applicable across neuropsychiatric disorders. Accumulating evidence from individual- and meta-studies in schizophrenia also highlights aberrant activity in the dorsal PFC and failure to deactivate DMN as the most consistent neural basis of cognitive impairments.[25,27–32] Studies comparing the neural activation during task performance among schizophrenia, bipolar disorder, and healthy controls show dorsal PFC abnormalities in both patient groups, that are most pronounced in schizophrenia.[30,33] These findings are in line with the generally more severe cognitive deficits in this group.[34,35] Furthermore, abnormal activity in dorsal PFC regions has been shown even broader across schizophrenia, unipolar disorder, bipolar disorder, anxiety disorders, and substance use disorders.[36,37] Finally, a meta-analysis and a systematic review of changes in neural activity in response to cognitive remediation treatments in schizophrenia found that enhanced activity in dorsal PFC and related neural circuits was the most reliable marker of cognitive improvements.[38,39] Similarly, a more recent longitudinal fMRI study in schizophrenia found that cognitive enhancement therapy was also accompanied by increased dorsolateral PFC activity, which was modestly associated with improved neurocognition.[40] Collectively, these findings support the notion that target engagement within dorsal PFC and DMN activity may be a putative transdiagnostic biomarker model for pro-cognitive effects.

For dorsal PFC and DMN target engagement to be a valid biomarker model for pro-cognitive effects, it must *fulfil five general validity criteria*[41,42]: it must (i) be sensitive to treatments with pro-cognitive effects, (ii) produce similar effects in patients with neuropsychiatric disorders and healthy controls, (iii) be sensitive to effective treatments with different mechanisms, (iv) be unresponsive to ineffective treatments, and (v) be sensitive to cognitive decline. Multiple fMRI studies indicate that the proposed biomarker model is sensitive to different pharmacological and psychological treatments with pro-cognitive effects across neuropsychiatric disorders,[21–24,38,40] thereby confirming criteria (i) and (iii). In a recent fMRI study, Macoveanu et al[42] found no treatment-related change in the dorsal PFC following an *ineffective* cognitive remediation trial, which supports validity criterion (iv). Although this finding supports the biomarker model validity, it requires replication in separate studies. Moreover, studies are now warranted to investigate criteria (ii) by testing the effects of pro-cognitive interventions in healthy populations and (v) by assessing the neural activity changes that accompany cognitive decline. If such studies support the validity of the proposed biomarker model for pro-cognitive effects, this would widen our understanding of brain mechanisms of effective treatments and impact treatment development strategies targeting cognition. Specifically, implementation of this biomarker model in small phase 2 trials could represent a much-needed tool to screen and select among novel candidate treatments for cognitive impairments, based on their ability to produce neurocircuitry target engagement prior to large-scale costly phase 3 efficacy trials.

Conclusions and Future Directions

There is a pressing need for new effective treatments targeting cognitive impairments across a range of neuropsychiatric

disorders. A key challenge in drug development strategies is the reliance upon preclinical biomarker models that have poor predictive validity of efficacy in humans. Identification of a human transdiagnostic neurocircuitry-based biomarker model of pro-cognitive effects can therefore have immense impact on the success rates of future treatment development. In this perspective article, we (i) reviewed a new model that can explain the variability in the findings regarding the *direction* of aberrant dorsal PFC activity across patients with mood disorders and treatment-related dorsal PFC activity change. Based on this model, we (ii) argue that normalization of dorsal PFC hypo- and hyper-activity and exaggerated DMN activity during cognitive performance is a strong candidate biomarker model for pro-cognitive effects across neuropsychiatric conditions. Lastly, we (iii) suggest the next steps to assess the validity of this putative transdiagnostic biomarker model are to investigate: (a) whether dorsal PFC and DMN activity change occurs with distinct treatments that improve cognition in healthy populations and other patient groups, and (b) whether ineffective treatments produce no activity change in these regions in additional patient groups, and (c) whether the opposite dorsal PFC and DMN changes occur with cognitive decline.

Acknowledgment. We would like to thank Miss Beata Trawińska for creating the figures.

Disclosures. Kamilla W. Miskowiak has received consultancy fees from Allergan and Janssen in the past 3 years. Kamilla W. Miskowiak is supported by a Lundbeck Foundation Fellowship (R215-2015-4121). Cecilia S. Petersen has no conflict of interest.

References

1. Millan MJ, Agid Y, Brune M, *et al.* Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012;**11**(2):141–168.
2. Etkin A, Gyurak A, O'Hara R. A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialog Clin Neurosci*. 2013;**15**(4):419–429.
3. Arguello PA, Gogos JA. Genetic and cognitive windows into circuit mechanisms of psychiatric disease. *Trends Neurosci*. 2012;**35**(1):3–13.
4. Martinez-Aran A, Vieta E. Cognition as a target in schizophrenia, bipolar disorder and depression. *Eur Neuropsychopharmacol*. 2015;**25**(2):151–157.
5. Tse S, Chan S, Ng KL, Yatham LN. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. *Bipolar Disord*. 2014;**16**(3):217–229.
6. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. *Eur J Neurol*. 2012;**19**(1):155–162.
7. Roiser JP, Sahakian BJ. Hot and cold cognition in depression. *CNS Spectr*. 2013;**18**(3):139–149.
8. Harvey PD, Sand M. Pharmacological augmentation of psychosocial and remediation training efforts in schizophrenia. *Front Psychiatry*. 2017;**8**:177.
9. Vreeker A, van Bergen AH, Kahn RS. Cognitive enhancing agents in schizophrenia and bipolar disorder. *Eur Neuropsychopharmacol*. 2015;**25**(7):969–1002.
10. Miskowiak KW, Burdick KE, Martinez-Aran A, *et al.* Methodological recommendations for cognition trials in bipolar disorder by the International Society for Bipolar Disorders Targeting Cognition Task Force. *Bipolar Disord*. 2017;**19**(8):614–626.
11. McIntyre RS, Cha DS, Soczynska JK, *et al.* Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013;**30**(6):515–527.
12. Millan MJ, Agid Y, Brune M, *et al.* Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov*. 2012;**11**(2):141–168.
13. National Institute of Mental Health. Research Domain Criteria (RDoC). https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/index.shtml. Accessed December 14 2019.
14. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*. 2013;**11**:126.
15. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014;**171**(4):395–397.
16. Kozak MJ, Cuthbert BN. The NIMH Research Domain Criteria initiative: background, issues, and pragmatics. *Psychophysiology*. 2016;**53**(3):286–297.
17. Insel T, Cuthbert B, Garvey M, *et al.* Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;**167**(7):748–751.
18. Morris SE, Cuthbert BN. Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialog Clin Neurosci*. 2012;**14**(1):29–37.
19. Miskowiak KW, Petersen CS. Neuronal underpinnings of cognitive impairment and—improvement in mood disorders. *CNS Spectr*. 2018;**24**:1–24.
20. Fossati P. EPA-0976—neural correlates of cognitive dysfunction in mood disorders. *Eur Psychiatry*. 2014;**29**(Supplement 1):1.
21. Miskowiak KW, Vinberg M, Glerup L, *et al.* Neural correlates of improved executive function following erythropoietin treatment in mood disorders. *Psychol Med*. 2016;**46**(8):1679–1691.
22. Meusel LA, Hall GB, Fougere P, McKinnon MC, MacQueen GM. Neural correlates of cognitive remediation in patients with mood disorders. *Psychiatry Res*. 2013;**214**(2):142–152.
23. Smith J, Browning M, Conen S, *et al.* Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. *Mol Psychiatry*. 2017;**23**:1127–1133.
24. Miskowiak KW, Macoveanu J, Vinberg M, *et al.* Effects of erythropoietin on memory-relevant neurocircuitry activity and recall in mood disorders. *Acta Psychiatr Scand*. 2016;**134**(3):249–259.
25. Callicott JH, Egan MF, Mattay VS, *et al.* Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry*. 2003;**160**(4):709–719.
26. Manoach DS. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophr Res*. 2003;**60**(2–3):285–298.
27. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry*. 2009;**66**(8):811–822.
28. Glahn DC, Ragland JD, Abramoff A, *et al.* Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Map*. 2005;**25**(1):60–69.
29. Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC. Prefrontal activation deficits during episodic memory in schizophrenia. *Am J Psychiatry*. 2009;**166**(8):863–874.
30. Hamilton LS, Altshuler LL, Townsend J, *et al.* Alterations in functional activation in euthymic bipolar disorder and schizophrenia during a working memory task. *Hum Brain Map*. 2009;**30**(12):3958–3969.
31. Pomarol-Clotet E, Salvador R, Sarro S, *et al.* Failure to deactivate in the prefrontal cortex in schizophrenia: dysfunction of the default mode network? *Psychol Med*. 2008;**38**(8):1185–1193.
32. Ortiz-Gil J, Pomarol-Clotet E, Salvador R, *et al.* Neural correlates of cognitive impairment in schizophrenia. *Br J Psychiatry*. 2011;**199**(3):202–210.
33. Costafreda SG, Fu CH, Picchioni M, *et al.* Pattern of neural responses to verbal fluency shows diagnostic specificity for schizophrenia and bipolar disorder. *BMC Psychiatry*. 2011;**11**:18.
34. Reichenberg A, Harvey PD, Bowie CR, *et al.* Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophr Bull*. 2009;**35**(5):1022–1029.
35. Barch DM. Neuropsychological abnormalities in schizophrenia and major mood disorders: similarities and differences. *Curr Psychiatry Rep*. 2009;**11**(4):313–319.
36. McTeague LM, Goodkind MS, Etkin A. Transdiagnostic impairment of cognitive control in mental illness. *J Psychiatr Res*. 2016;**83**:37–46.

37. McTeague LM, Huemer J, Carreon DM, Jiang Y, Eickhoff SB, Etkin A. Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am J Psychiatry*. 2017;**174**(7):676–685.
38. Ramsay IS, MacDonald AW 3rd. Brain correlates of cognitive remediation in schizophrenia: activation likelihood analysis shows preliminary evidence of neural target engagement. *Schizophr Bull*. 2015;**41**(6): 1276–1284.
39. Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. *Socioaffect Neurosci Psychol*. 2016;**6**:30054.
40. Keshavan MS, Eack SM, Prasad KM, Haller CS, Cho RY. Longitudinal functional brain imaging study in early course schizophrenia before and after cognitive enhancement therapy. *NeuroImage*. 2017;**151**:55–64.
41. Harmer CJ, Cowen PJ, Goodwin GM. Efficacy markers in depression. *J Psychopharmacol*. 2011;**25**(9):1148–1158.
42. Macoveanu J, Demant KM, Vinberg M, Siebner HR, Kessing LV, Miskowiak KW. Towards a biomarker model for cognitive improvement: no change in memory-related prefrontal engagement following a negative cognitive remediation trial in bipolar disorder. *J Psychopharmacol*. 2018; **32**:1075–1085.