Influence of pre-treatment structural brain measures on effects of action-based cognitive remediation on executive function in partially or fully remitted patients with bipolar disorder

MB Mogensen\textsuperscript{a}, J Macoveanu\textsuperscript{a}, GM Knudsen\textsuperscript{c,d}, CV Ott\textsuperscript{a}, KW Miskowiak\textsuperscript{a,b,*}

\textsuperscript{a} Neurocognition and Emotion in Affective Disorder (NEAD) Group, Copenhagen Affective Disorder research Centre (CADIC), Psychiatric Centre Copenhagen, Copenhagen University hospital, Rigshospitalet, Denmark
\textsuperscript{b} Department of Psychology, University of Copenhagen, Copenhagen, Denmark
\textsuperscript{c} Neurobiology Research Unit, Copenhagen University Hospital, Rigshospitalet
\textsuperscript{d} Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Received 30 September 2021; received in revised form 24 November 2021; accepted 26 November 2021

KEYWORDS
Cognitive impairment; Randomized controlled trial; Cognitive remediation; structural MRI; Dorsal prefrontal cortex; Bipolar disorder

Abstract
Cognitive impairment is an emerging treatment target in patients with bipolar disorder (BD) but so far, no evidence-based treatment options are available. Recent studies indicate promising effects of Cognitive Remediation (CR) interventions, but it is unclear who responds most to these interventions. This report aimed to investigate whether pre-treatment dorsal prefrontal cortex (dPFC) thickness predicts improvement of executive function in response to Action-Based Cognitive Remediation (ABCR) in patients with BD. Complete baseline magnetic resonance imaging (MRI) data were available from 45 partially or fully remitted patients with BD from our randomized controlled ABCR trial (ABCR: $n = 25$, control group: $n = 20$). We performed cortical reconstruction and volumetric segmentation using FreeSurfer. Multiple linear regression

\* Corresponding author at: Neurocognition and Emotion in Affective Disorder (NEAD) Group, Copenhagen Affective Disorder Research Centre, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, and Department of Psychology, University of Copenhagen, Øster Farimagsgade 2A, DK-1353 Copenhagen, Denmark
E-mail address: kamilla.miskowiak@regionh.dk (K. Miskowiak).

https://doi.org/10.1016/j.euroneuro.2021.11.010
0924-977X/© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
1. Introduction

Cognitive impairment is an emerging treatment target in patients with mood disorders, due to the close association between cognitive impairment and functional disability (Bonnin et al., 2019; Tse et al., 2014). In particular, studies have shown that cognitive impairment has a major impact on psychosocial function, including occupational outcome, quality of life and socio-economic burden of these disorders (Bonnin et al., 2019; Depp et al., 2012; Legemaat et al., 2021). In the past decade, there has been an immense research interest in the development of treatments targeting these impairments, but so far treatment success has been limited (Legemaat et al., 2021; Tsapekos et al., 2020). However, promising new evidence from cognitive remediation (CR) studies indicate benefits on cognitive abilities and functional outcomes in bipolar disorder (BD) (Tsapekos et al., 2020). Further, meta-analytic evidence revealed a medium effect size for CR in major depressive disorder (MDD) (Legemaat et al., 2021).

Across CR trials, executive functions including planning, inhibition, flexibility and reasoning are a common treatment target, and this domain responds most consistently to CR across different trials (Penadés et al., 2019; Tsapekos et al., 2020). In agreement with this, a study of Action-Based Cognitive Remediation (ABCR) by our group, revealed a strong effect on executive function (the key secondary outcome), but not on global cognition (Ott et al., 2020). However, we currently have little insight into which patient characteristics predict greater cognitive benefits in response to CR, which would be important for future pre-screening for these interventions.

Some studies suggest that greater cognitive impairment at baseline is a predictor of treatment response on cognition to both CR and pharmacological treatments (Burlick et al., 2012; Ott et al., 2016). In accordance with this, we observed that deficits within executive function at baseline was associated with greater treatment effects of ABCR in this domain in BD (Ott et al., 2020, 2021). These findings convergence with the recent recommendations by the International Society for Bipolar Disorders (ISBD) Targeting Cognition Task Force, to pre-screen for cognitive impairments within the domains targeted by the intervention (Miskowiak et al., 2017). Further, emerging evidence from functional magnetic resonance imaging (fMRI) indicates that pre-treatment hypo-activity in dorsal prefrontal cortex (dPFC) predicts greater treatment response to CR in patients with mood disorders (Miskowiak et al., 2021). Nevertheless, little is known about whether pre-treatment structural brain measures are associated with treatment success of CR interventions.

Executive function is a multifaceted domain that determines the capacity to generate plans, maintain focus to follow through with these, and flexibility to change them in response to changing contingencies (Suchy 2009). The level of executive function depends on the integrity of the dorsal prefrontal cortex (dPFC), with smaller dPFC volume and thickness being associated with impaired executive performance in general (Miller and Cohen 2001; Ronan et al., 2020; Yuan and Raz 2014). In schizophrenia and BD, executive function impairment has been associated with lower dPFC volume and cortical thickness, respectively (Boniila et al., 2008; Fears et al., 2015). In contrast, emerging evidence from two recent studies found that in remitted patients recently diagnosed with BD, cognitive deficits were accompanied by greater dPFC volume and/or thickness as well as white matter abnormalities (Chakrabarty et al., 2021; Macoveanu et al., 2021). These findings were interpreted as a result of compensatory dPFC recruitment to maintain mood stability or, alternatively, failure of pruning during neurodevelopment (Chakrabarty et al., 2021; Macoveanu et al., 2021).

Taken together, abnormalities in dPFC seem to be a key structural correlate of executive function impairments across patients with neuropsychiatric disorders, and thus a possible treatment target to improve executive functioning. Accordingly, a study of patients with schizophrenia showed that a larger pre-treatment cortical volume and surface area was associated with greater response to CR (Keshavan et al., 2011). Consistent with this, another study found that more pre-treatment cortical thickness in frontal and temporal regions was associated with greater CR-related cognitive improvement in schizophrenia (Penadés et al., 2016, 2019). However, no studies to date have investigated whether pre-treatment structural brain measures influence cognitive benefits of CR in mood disorders. To improve targeting of CR to those with greatest scope for efficacy, insight into characteristics of patients with mood disorders that potentially could predict stronger effects of CR is needed. Notably, MRI may due to its high cost be most relevant in research settings. Regarding its clinical potential, a cost-benefit analysis would be warranted to clarify whether the cost of MRI may be outweighed by the...
potential to aid tailoring of treatments and thereby improve patient outcomes.

Since ACR specifically improved executive function measured with the One Touch Stockings of Cambridge (OTS) (secondary outcome), we here aimed to investigate whether dPFC thickness is associated with treatment efficacy of ACR on this domain based on structural neuroimaging data collected at baseline for BD patients in our ACR trial (Ott et al., 2020). Based on the preliminary evidence from CR study in schizophrenia, we tentatively hypothesised that greater dPFC thickness at baseline would be associated with more ACR-related improvement in executive function. To test the hypothesis, we used linear regression to investigate the interaction between dPFC thickness and treatment efficacy. In addition, we conducted a vertex wise cortical surface analysis to examine whether the cortical volume and thickness in other brain regions were associated with response to ACR.

2. Experimental procedures

2.1. Study participants

Patients were recruited from the Copenhagen Affective Disorder Clinic and consultant psychiatrists in the Capital Region of Denmark. The patients were randomized with stratification for gender and age (≥35 or ≥35) to either 10 weeks of group-based ACR treatment twice a week (active) or weekly unstrucntured group sessions (control). The inclusion criteria consisted of: a BD diagnosis (type I or II) based on ICD-10 criteria confirmed using the Schedules for Clinical Assessment in Neuropsychiatry interview (SCAN) (Wing et al., 1990), full or partial remission (full remission: ≤7, partial remission:8–14 on Hamilton Depression Rating 17-items Scale (HDRS) (Hamilton 1960) and the Young Mania Rating Scale (YRMS) (Young et al., 1978)), age between 18 and 55 years, fluency in Danish and objective cognitive impairments measured on the Screen for Cognitive Impairment in Psychiatry (SCIP) (Jensen et al., 2015), as reflected by either a total score of 74 or below, or a score below defined cut-off values on minimum two of the five subtests. Exclusion criteria were: dyslexia, severe somatic illness, daily use of benzodiazepines ≥2.5 mg, current alcohol or drug abuse, neurological illness, schizophrenia or a schizoaffective disorder, previous severe head trauma, pregnancy, pacemaker or other metal implants, and electroconvulsive treatment within the past three months. For more details see (Ott et al., 2018).

2.2. Intervention

For at detailed description of the ACR intervention, please see (Ott et al., 2018). In brief, patients allocated to ACR received individual goal setting sessions, two-hour group sessions twice weekly over 10 weeks, and daily computer trainings at home. The group sessions included practical and computerized trainings that simulated everyday activities (e.g. remembering people’s names, structuring one’s calendar etc.) and a goal setting discussion. Thus, the program specifically covered several cognitive domains, including executive functions; organization, shifting attention and planning. Patients allocated to the control group underwent a 10-week program with weekly 1 h group sessions, that consisted of unstructured conversations guided by a therapist, discussing themes relevant to patients but with no cognitive training aspects.

2.3. Procedures

The participants underwent neuropsychological testing and magnetic resonance imaging (MRI) scans at baseline and after two weeks of treatment, and neuropsychological testing again at treatment completion. All assessments were conducted by blinded assessors. Results from the two-week MRI scan are reported elsewhere (Ott et al., 2021). For more details on the study procedure and power calculation see (Ott et al., 2018). Written consent was obtained from all patients, and thorough information about the study procedures was given before. The study was approved by the local ethics committee (H-16,043,480) and the Danish Data Protection Agency (2012-58-0004).

2.4. Structural magnetic resonance imaging protocol

Whole-brain structural MRI data were acquired at Rigshospitalet, Copenhagen, using a 3 Tesla Siemens Prisma scanner (Siemens Trio, Erlangen, Germany) with a 64-channel head-neck coil. T1-weighted structural images were acquired using a 3D MPRAGE sequence (FOV=230 x 230 mm, slice thickness=0.9 mm, TR=1900 ms; TE=2.58 ms; flip angle=9°; distance factor=50%). All scans were corrected for B0 field geometric distortions and visually inspected to ensure good image quality and rule out overt structural brain abnormalities or artefacts.

2.5. Neuropsychological testing and end point

The end point was change in OTS ‘mean choices to correct’ from the Cambridge Neuropsychological Test Automated Battery (CANTAB), since ACR treatment specifically improved this measure of executive function in the original trial (Ott et al., 2020). The OTS change scores were calculated by subtracting OTS scores at treatment completion from OTS scores at baseline, with positive change scores on the OTS ‘mean choices to correct’ reflecting improved performance.

2.6. Statistical analysis

2.6.1. Patient characteristics analyses

Patient groups were compared on clinical and demographical information at baseline using independent t-tests or Mann-Whitney depending on the distribution of the variables. For categorical variables we used chi-squared (χ²)-tests to compare groups.

2.6.2. Linear regression analysis and predictor variables

Linear regression analysis was carried out with change in OTS as the endpoint. We included the following predictor variables: treatment (ABCR/control), dPFC thickness computed with FreeSurfer software (details later), the interaction between dPFC thickness and treatment, total intracranial volume (TIV), age, lithium treatment (yes/no), educational years and gender. The rationale for including education years as a covariate was evidence for an association between number of educational years and a larger cortical thickness (Ritchie et al., 2018). Lithium treatment was included as a covariate due to evidence for an association between lithium and greater cortical thickness that may represent neurotrophic effects (Hibar et al., 2018) and could hence represent greater propensity for neuroplastic change and cognitive improvement. All analyses were conducted in IBM Statistical Package for the Social Sciences version 25.0 (SPSS Inc.). Results were considered significant at p<0.05.
2.7. Vertex-wise analysis of the cortical thickness and volume

Cortical reconstruction and volumetric segmentation were performed using the FreeSurfer image analysis suite v7.1.0 (http://surfer.nmr.mgh.harvard.edu/). Individual B0 field distortion corrected T1-weighted images were processed with the standard FreeSurfer pipeline which included correction for intensity non-uniformity, intensity normalization, skull strip, and automatic segmentation of the cortical and subcortical grey-matter structures including the hippocampi as documented here (Dale et al., 1999; Fischl et al., 2002). Surface-based data created by the processing pipeline included representations of cortical thickness and volume. The quality of the cortical reconstructions was assessed by visual inspection and edits were carried out when needed. The estimated TIV, computed by the automated FreeSurfer segmentation, was extracted and used to remove the effect of an individual’s brain size.

To test our hypothesis regarding dorsal PFC, we constructed bilateral dorsal PFC masks by adding the superior frontal, rostral and caudal middle frontal gyri from the automated cortical parcellation according to the Desikan-Killiany Atlas (Desikan et al., 2006). In a vertex-wise analysis we tested for differential change between ABCR and control groups in OTS scores, regressing out the effect of age, sex and TIV. For this, vertex thickness or vol-

---

**Fig. 1** CONSORT flow-chart.
ume were entered in respective General Linear Models (GLMs) with group as fixed factor and change in OTS scores, age, sex and TIV as covariates. We secondly conducted analogue analyses to explore group differences in the entire cortex. Cluster-wise significance was assessed at p<0.05 following correction for vertex-wise multiple comparisons within respective search volumes, conducted using Monte Carlo null-z simulations based on precomputed simulation data in FreeSurfer and a cluster forming threshold of p<0.001.

3. Results

3.1. Patient characteristics

Of the 64 patients who were randomized, 45 had complete pre-treatment MRI data, and OTS data form both baseline and post-treatment (ABCR: n = 25, control: n = 20) (Fig. 1: CONSORT flowchart). The ABCR and control groups were well-matched on all demographic and clinical variables (ps≥0.06) (Table 1).

4. Linear regressions

Is dorsal prefrontal cortex thickness at baseline associated with improvement in executive function after ABCR treatment?

The linear model explained a significant proportion of the variance in executive improvement (adjusted R²=0.35; F(8,36)=3.92, p = 0.002). As expected, there was a main effect of treatment (ABCR, Control) with ABCR being associated with improvement of executive function over time (Treatment: β=16.79, 95% CI [1.34;32.23], p = 0.034) (Table 2).

In addition, there was a main effect of lithium indicating that concomitant lithium treatment, independent of group, was associated with less improvement in executive function over time (Lithium: β=−1.04, 95% CI [−1.67;−0.40], p = 0.002) (Table 2). This effect of lithium occurred in the absence of any baseline differences in executive function between lithium treated and non-lithium treated patients (p = 0.44).

Importantly, the model showed that lower pre-treatment dPFC thickness was associated with better treatment response on executive function after ABCR vs. control treatment, independent of age, gender, education level and lithium treatment (Treatment × dPFC thickness: β=−5.92, 95% CI [−10.87;−0.97], p = 0.02) (Table 2, Fig. 2).

Does pre-treatment cortical volume and thickness influence treatment response from ABCR?

The whole cortex volume analysis revealed a significant interaction effect between right superior temporal gyrus volume and treatment (ABCR, control) on improvement in OTS performance (Fig. 3). Specifically, lower pre-treatment superior temporal gyrus volume was associated with greater ABCR-related improvement on the OTS in analyses adjusted for age, gender and TIV. In contrast, analysis of dorsal PFC volume revealed no regions with a significant influence on

| Table 1 Patient Characteristics. |
|----------------------------------|
| Patient demographic and clinical characteristics |
| Characteristic | ABCR (n = 25) | Control (n = 20) | p value |
|----------------|---------------|-----------------|---------|
| Age, years, mean ± SD | 37 ± 12 | 36 ± 12 | 0.85 |
| Gender, (F/M%) | 76/24 | 80/20 | 0.75 |
| Educational years, mean ± SD | 13 ± 3 | 14 ± 3 | 0.27 |
| OTS Baseline, mean ± SD | 1.39±0.27 | 1.39±0.20 | 0.97 |
| OTS Change, mean ± SD | 0.84 ± 1.16 | −0.08 ± 1.06 | 0.008 |
| TIV, mm³, mean ± SD | 1520,411.45 | 1499,220.48 | 0.62 |
| β | 12.39 | 11.56 | 0.85 |
| DART IQ, mean ± SD | 111 ± 6 | 111 ± 8 | 0.93 |
| HDRS, mean ± SD | 7 ± 4 | 6 ± 4 | 0.39 |
| YMRS, mean ± SD | 3 ± 4 | 3 ± 4 | 0.60 |
| BD type (I/I%) | 32/68 | 35/65 | 0.83 |
| Illness duration, years, mean ± SD | 16 ± 12 | 15 ± 9 | 0.60 |
| Age at diagnosis, years, mean ± SD | 35 ± 12 | 32 ± 10 | 0.45 |
| Number of depressive episodes, mean ± SD | 7 ± 5 | 10 ± 10 | 0.23 |
| Number of manic or hypomanic episodes, mean ± SD | 6 ± 8 | 5 ± 7 | 0.44 |
| Medication: | | | |
| Antidepressants, no. (%) | 2(8) | 6 (30) | 0.06 |
| Antipsychotics, no. (%) | 11 (44) | 10 (50) | 0.69 |
| Anticonvulsants, no. (%) | 15 (60) | 13 (65) | 0.73 |
| Lithium, no. (%) | 15(60) | 10 (50) | 0.50 |
| None, no. (%) | 1 (4) | 1 (5) | 0.87 |

Abbreviations: SD=Standard Deviation, DART=Danish Adult Reading test, HDRS=Hamilton Depression Rating Scale, YMRS=Young Mania Rating Scale, BD type=Bipolar Disorder type, OTS = One Touch Stockings of Cambridge: ‘mean choices to correct’, TIV=Total Intercranial Volume.
Table 2  Linear Regression Models.

| Variable                  | Estimate, β (95% CI) | p value |
|---------------------------|----------------------|---------|
| Intercept                 | −3.63 (−15.35 to 8.08) | 0.533   |
| Age                       | 0.02 (−0.006 to 0.05)  | 0.126   |
| Gender                    | −0.016 (−0.87 to 0.83) | 0.97    |
| Education level           | 0.038 (−0.063 to 0.14) | 0.45    |
| TIV                       | 1.51 × 10⁻⁶           | 0.27    |
| Lithium                   | −1.04 (−1.67 to −0.40) | 0.002   |
| Treatment                 | 16.79 (1.34 to 32.23)  | 0.034   |
| Treatment*dPFC thickness   | −5.92 (−10.87 to −0.97) | 0.02    |

Abbreviations: TIV = Total intracranial volume, dPFC = dorsal prefrontal cortex.

Fig. 2  Illustration of dPFC area, for which pre-treatment cortical thickness was associated with response to ABCR on executive function, measured with One Touch Stockings of Cambridge (OTS) (left) and graph over the association between dPFC thickness and ABCR-related OTS improvement (right, OTS improvement = OTS baseline - OTS post treatment). Values are adjusted for age, sex, TIV, lithium, years of education.

Fig. 3  Illustration of superior temporal cortex region, for which pre-treatment volume influence response to ACRB on executive function, measured with One Touch Stockings of Cambridge (OTS) (left, OTS improvement = OTS baseline - OTS post treatment) and graph illustrating this association (right). Values are adjusted for age, sex, and TIV.

ABCR-related improvement in OTS performance. Analysis of the cortical thickness at a whole-brain level also revealed no regions that significantly influenced ABCR effects on OTS performance.

5. Discussion

This is the first report to investigate whether pre-treatment dPFC thickness influences treatment effects of a CR inter-
vention, ABCR, on executive function in fully or partially remitted patients with BD. Contrary to our hypothesis, we found that less pre-treatment dPFC thickness was associated with greater response to ACR on executive function, measured with the OTS (the secondary trial outcome that was significantly improved by ACR). In keeping with this, exploratory whole-brain vertex analysis revealed an association between lower superior temporal gyrus volume and more ACR-related improvement of executive function. This influence of pre-treatment dPFC thickness and superior temporal volume on response to ACR on executive function was observed in analyses adjusted for demographic and clinical variables and TIV. Finally, while lithium and non-lithium-treated patients showed no baseline difference in executive function, those treated with lithium showed less executive improvement over time, irrespective of treatment.

Insight into whether pre-treatment structural brain measures influence the response to pro-cognitive interventions in neuropsychiatric disorders is limited. Emerging findings from a few neuroimaging studies of CR in schizophrenia found that greater dPFC and superior temporal cortical volume and/or thickness were associated with more CR-associated improvements of cognitive functions including verbal and visual memory and social cognition (Keshavan et al., 2011; Penadés et al., 2016, 2019). This was interpreted as an indication that greater structural brain integrity facilitated patients’ ability to benefit from CR, because of the illness-related frontal-temporal cortical thinning (Crespo-Facorro et al., 2011; Kuperberg et al., 2003; Nesvåg et al., 2008) and its association with more cognitive impairments (Hartberg et al., 2011). The opposite association in our sample of ACR-treated BD patients with more ACR related improvement of executive function in patients with lower dPFC thickness, was therefore unexpected, although no studies to date investigated whether pre-treatment structural measures influence the response to CR in BD.

Cognitive impairments in BD and schizophrenia are thought to involve shared underlying brain pathology because of the common genetic liability (Lichtenstein et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014) and similar profiles of neurocognitive impairments across the disorders (Lewandowski et al., 2011). However, there is also evidence to suggest partially distinct brain structure correlates of cognitive impairments in BD and schizophrenia, respectively. A largescale study of brain-cognition associations in the two illnesses found a positive association between left temporal cortex thickness and cognitive function in schizophrenia, but a negative association between right temporal cortex thickness and cognition in BD (Hartberg et al., 2011). These differences may indicate distinct neuropathological origins of cognitive impairments in BD and schizophrenia and could explain the opposite directions of the associations between structural dPFC and superior temporal measures and CR-related cognitive improvements in these disorders.

Indeed, greater residual ‘brain reserve’ may be needed for patients with schizophrenia to benefit from CR, given their more severe neuropathological changes (Birur et al., 2017) and greater associated cognitive deficits (Daban et al., 2006). In contrast, patients with BD generally show less extensive brain and cognition changes and may thus benefit more from CR when they present with a certain degree of dPFC or temporal cortex abnormalities, which can be targeted and restored through CR. In line with this interpretation, we found that patients with the lowest pre-treatment OTS performance (Ott et al., 2021) and most working memory-related dPFC hypo-activity (Miskowiak et al., 2021) showed the greatest treatment benefits of ACR on executive function. Alternatively, given the suggestion that larger dPFC thickness in BD may indicate failure of pruning during neurodevelopment (Chakrabarty et al., 2021; Macoveanu et al., 2021), the association between lower dPFC thickness and response to ACR could, in fact, be in line with the hypothesized relation between structural brain integrity and propensity to benefit from CR (Keshavan et al., 2011; Penadés et al., 2016). The observed association between lower superior temporal gyrus volume and greater cognitive benefits of ACR is in keeping with this interpretation, given evidence that lower temporal pole thickness is linked to better working memory performance in BD (Hartberg et al., 2011).

Finally, a possible alternative explanation for the divergent associations between pre-treatment brain structure and response to CR in our BD sample and in schizophrenia is the different CR interventions and outcome measures. Specifically, ACR involved an extensive focus on training of executive function (including planning, goal setting, structuring, monitoring, and organizing daily cognitively challenging tasks) and, consequently, produced robust executive function improvement. Conversely, CR in schizophrenia involved more broad cognitive training of frontal, executive and social skills and resulted in improvements in nonverbal and visuospatial memory and socio-cognitive functions (Keshavan et al., 2011; Penadés et al., 2016). Nevertheless, given the scarcity of studies of structural brain predictors of cognitive response to CR, the differential associations between structural brain measures and cognitive benefits of CR in BD and schizophrenia, respectively, warrant further investigation. Notably, the influence of dPFC thickness on treatment efficacy was observed only in the analysis using the PFC ROI for small volume correction, suggesting that the effect was subtle.

Treatment modality may play a role in prediction of treatment efficacy on cognition based on pre-treatment structural brain measures in BD. In a pharmacological intervention study of the effects of eight weeks of erythropoietin (EPO) vs. saline on cognition in patients with mood disorders (BD or MDD), larger pre-treatment cortical surface and hippocampal asymmetry predicted greater EPO-related improvement of global cognition (Miskowiak et al., 2020). This was interpreted as an indication that greater structural brain integrity (or ‘brain reserve’) increased patients’ propensity to benefit from a biological intervention that stimulates neuroplasticity (Miskowiak et al., 2020). The opposite findings in our ACR trial may at first seem counterintuitive, however, this pattern of discrepant brain-cognition response associations is in line with emerging evidence for opposite associations between neuroimaging predictors of treatment efficacy on mood symptoms of psychological and pharmacological interventions respectively (Seeberg et al., 2018). Pharmacological interventions restore brain function and structure in an automatic way, and ‘less abnormal’ brains may thus be more easily re-
stored. In contrast, psychological interventions including CR involve effortful recruitment of neuronal resources through intensive ‘plasticity-based’ training (Vinogradov et al., 2012). Hence, for CR interventions, less pre-treatment dPFC thickness and temporal cortex volume might leave more ‘room for growth’ (i.e., greater neuropsychiatric change), and hence predict greater training-related cognitive improvement. In keeping with this, structural increases of cortical and limbic regions seem to be key mechanisms of CR in schizophrenia (Eack et al., 2010; Morimoto et al., 2018), although notably no longitudinal structural imaging studies have been conducted of CR in BD. Nevertheless, this interpretation must be considered hypothetical given the paucity of studies of structural neuroimaging predictors of treatment response to pro-cognitive interventions in BD.

We had included lithium as a covariate because of emerging evidence for increased cortical thickness with lithium use (Hibar et al., 2018). Unexpectedly, this revealed a cognitive decline over time in patients receiving lithium, independent of intervention (ABCR/control). In the literature, findings regarding the effect of lithium on executive function are conflicting (Paterson and Parker, 2017). Given the relatively small sample size, further studies are needed to determine the effect of lithium use on the trajectory of executive function.

A study limitation was the modest sample size (n = 45), that did not allow for more complex analyses of additional potential predictors (such as illness duration and types of comorbid medications) without compromising the statistical power. Furthermore, the report is based on a group finding, and the clinical implications for individual patients are limited. This report was a secondary exploratory analysis of our original ABCR trials, and our certainty is thus limited by the absence of replication studies. It was also a limitation that doses of patients’ concomitant pharmacological treatments had not been recorded. A strength was that the analyses were based on a randomized controlled trial showing post-treatment effect of ABCR on executive function with a large effect size, thus allowing for an investigation of specific baseline predictors of treatment efficacy on this cognitive domain. Finally, it should be mentioned that we investigated baseline fMRI and cognitive predictors of ABCR-related cognitive improvement in a previous report (Miskowiak et al., 2021), and that the current findings regarding structural MRI predictors should only be considered hypothesis-generating due to their exploratory nature and lack of correction for multiple comparisons.

In conclusion, we demonstrated that lower pre-treatment dPFC thickness and superior temporal volume was associated with greater ABCR treatment efficacy on executive function in fully or partially remitted patients with BD. The influence of dPFC thickness and superior temporal volume on ABCR efficacy is in line with previous findings that pre-treatment cognitive impairment as well as working memory-related hypo-activity predict greater cognitive benefits of CR and pharmacological interventions targeting cognition. Future studies are warranted to investigate whether the observed associations can be replicated with other treatments targeting cognitive impairment and other neuropsychiatric illnesses.

**Author disclosures**

**Role of funding source**

The study was supported by the Lundbeck Foundation (grant R215-20154121) awarded to Kamilla Miskowiak; the Lundbeck Foundation had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

**Contributors**

KWM and CVO designed the original intervention trial, conducted the analyses and collected the data. KMW designed the present study and analysis protocol and conducted the statistical analyses. MBM managed the literature searches and wrote the first draft of the manuscript together with KWM. JM undertook the analysis and processing of structural MRI data. All authors contributed to, critically reviewed and approved the final manuscript.

**Conflict of interest**

KWM has received honoraria from Janssen-Cilag and Lundbeck in the past three years. MBM, JM, CVO and GMK report no conflicts of interest.

**Acknowledgements**

We wish to acknowledge Emilie Poulsen, psychologist from Neurocognition and Emotion in Affective Disorder (NEAD) Group, for assistance with proof reading.

**References**

Birur, B., Kraguljac, N.V., Shelton, R.C., Lahti, A.C., 2017. Brain structure, function, and neurochemistry in schizophrenia and bipolar disorder—a systematic review of the magnetic resonance neuroimaging literature. NPJ Schizophr. 3 (1), 15. doi:10.1038/s41537-017-0013-9.

Bonilha, L., Molnar, C., Horner, MD., Anderson, B., Forster, L., George, MS., Nahas, Z., 2008. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. Schizophr. Res. 101 (1-3), 142-151. doi:10.1016/j.schres.2007.11.023.

Bonnin, C.M., Reinares, M., Martínez-Arán, A., Jiménez, E., Sánchez-Moreno, J., Solé, B., Montejo, L., Vieta, E., 2019. Improving functioning, quality of life, and well-being in patients with bipolar disorder. Int. J. Neuropsychopharmacol. pyz2018. doi:10.1093/ijnp/pyx2018.

Burdick, KE., Braga, RJ., Nnadi, CU., Shaya, Y., Stearns, WH., Malhotra, AK., 2012. Placebo-controlled adjunctive trial of primipexole in patients with bipolar disorder: targeting cognitive dysfunction. J. Clin. Psychiatry 73 (01), 103-112. doi:10.4088/JCP.11m07299.

Chakrabarty, T., Torres, IJ., Su, WW., Sawatzky, R., Keramatian, K., Yatham, LN., 2021. Cognitive subgroups in first episode bipolar I disorder: relation to clinical and brain volumetric variables. Acta Psychiatr. Scand. 143 (2), 151-161. doi:10.1111/acps.13245.
Miskowiak, Kw, Burdick, Ke, Martinez-Aran, A., Bonnin, Cm, Bowir, Cr, Carvalho, Af, Gallagher, P., Lafer, B., Lopez-Jaramillo, C., Sumiyoshi, T., McIntyre, Rs, Schaffer, A., Porter, Rj, Torres, Ij, Yatham, Ln, Young, Ah, Kessing, Lvm, Vieta, E., 2017. Methodological recommendations for cognition trials in bipolar disorder by the international society for bipolar disorders targeting cognition task force. Bipolar Disord. 19 (8), 614-626. doi:10.1111/bdi.12534.

Morimoto, T., Matsuda, Y., Matsuoka, K., Yasuno, F., Ikebuchi, E., Kameda, H., Taoka, T., Miyasaka, T., Kichikawa, K., Kishimoto, T., 2018. Computer-assisted cognitive remediation therapy increases hippocampal volume in patients with schizophrenia: a randomized controlled trial. BMC Psychiatry 18 (1), 83. doi:10.1186/s12888-018-1667-1.

Nesvåg, R., Lawyer, G., Varnäs, K., Fjell, Am, Walhovd, KB., Frigessi, A., Jonsson, EG., Agartz, I., 2008. Regional thinning of the cerebral cortex in schizophrenia: effects of diagnosis, age and antipsychotic medication. Schizophr. Res. 98 (1-3), 16-28. doi:10.1016/j.schres.2007.09.015.

Ott, CV., Macoveanu, J., Bowie, Cr., Fisher, PM., Knudson, GM., Kessing, Lvm, Miskowiak, Kw., 2021. Change in prefrontal activity and executive functions after action-based cognitive remediation in bipolar disorder: a randomized controlled trial. Neuropsychopharmacology 46 (6), 1113-1121. doi:10.1038/s41386-020-00901-7.

Ott, CV., Vinberg, M., Bowie, Cr., Christensen, E.M., Knudson, GM., Kessing, Lvm, Miskowiak, Kw., 2018. Effect of Action-based cognitive remediation on cognition and neural activity in bipolar disorder: study protocol for a randomized controlled trial. Trials 19 (1), 487. doi:10.1186/s13063-018-2860-8.

Ott, CV., Vinberg, M., Kessing, Lvm, Bowie, Cr., Forman, Jl., Miskowiak, Kw., 2020. Effect of action-based cognitive remediation on cognitive impairment in patients with remitted bipolar disorder: a randomized controlled trial. Bipol. Disord. doi:10.1111/bdi.13021.

Ott, C.V., Vinberg, M., Kessing, Lvm, Miskowiak, Kw., 2016. The effect of erythropoietin on cognition in affective disorders - associations with baseline deficits and change in subjective cognitive complaints. Eur. Neuropsychopharmacol. 26 (8), 1264-1273. doi:10.1016/j.euroneuro.2016.05.009.

Paterson, A., Parker, G., 2017. Lithium and cognition in those with bipolar disorder. Int. Clin. Psychopharmacol. 32 (2), 57-62. doi:10.1097/YIC.000000000000152.

Penadés, R., Franck, N., González-Vallespi, L., Dekerle, M., 2019. Neuroimaging studies of cognitive function in schizophrenia. In: Guest, P.C., (Ed.), Reviews On Biomarker Studies in Psychiatric and Neurodegenerative Disorders. In: Advances in Experimental Medicine and Biology, Vol. 1118. Cham: Springer International Publishing, pp. 117-134.

Penadés, R., Pujol, N., Catalán, R., Masana, G., García-Rizo, C., Bargalló, N., González-Rodríguez, A., Vidal-Piñeiro, D., Bernado, M., Junqué, C., 2016. Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia. Schizophr. Res. 171 (1-3), 110-116. doi:10.1016/j.schres.2016.01.006.

Ritchie, SJ., Dickie, D.A., Cox, SR., Hernández, MC.V, Sibbett, R., Pattie, A., Anblagan, D., Redmond, P., Royle, NA., Corley, J., Maniega, S.M., Taylor, AM., Karama, S., Booth, T., Gow, AJ., Starr, JM., Bastin, ME., Wardlaw, JM., Deary, IJ., 2018. Brain structural differences between 73- and 92-year olds matched for childhood intelligence, social background, and intracranial volume. Neurobiol. Aging 62, 146-158. doi:10.1016/j.neurobiolaging.2017.10.005.

Ronan, L., Alexander-Bloch, A., Fletcher, P.C., 2020. Childhood obesity, cortical structure, and executive function in healthy children. Cereb. Cortex 30 (4), 2519-2528. doi:10.1093/cercor/bhz257.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511 (7510), 421-427. doi:10.1038/nature13595.

Seeberg, L., Kjaerstad, HL., Miskowiak, KW., 2018. Neural and behavioral predictors of treatment efficacy on mood symptoms and cognition in mood disorders: a systematic review. Front. Psychiatry 9, 337. doi:10.3389/fpsyt.2018.00337.

Suchy, Y., 2009. Executive functioning: overview, assessment, and research issues for non-neuropsychologists. Ann. Behav. Med. 37 (2), 106-116. doi:10.1007/s12160-009-9097-4.

Tsapekos, D., Seccomandi, B., Mantingh, T., Cella, M., Wykes, T., Young, AH., 2020. Cognitive enhancement interventions for people with bipolar disorder: a systematic review of methodological quality, treatment approaches, and outcomes. Bipolar Disord. 22 (3), 216-230. doi:10.1111/bdi.12848.

Tse, S., Chan, S., Ng, K.L., Yatham, LN., 2014. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. Bipolar Disord. 16 (3), 217-229. doi:10.1111/bdi.12148.

Vinogradov, S., Fisher, M., de Villiers-Sidani, E., 2012. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology 37 (1), 43-76. doi:10.1038/nnp.2011.251.

Wing, J.K., Baboor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN: schedules for clinical assessment in neuropsychiatry. Arch. Gen. Psychiatry 47 (6), 589. doi:10.1001/archpsyc.1990.01810180089012.

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133 (5), 429-435. doi:10.1192/bjp.133.5.429.

Yuan, P., Raz, N., 2014. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. Neurosci. Biobehav. Rev. 42, 180-192. doi:10.1016/j.neubiorev.2014.02.005.