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Action-based cognitive remediation in bipolar disorder improved verbal memory but had no effect on the neural response during episodic memory encoding

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\textbf{ABSTRACT}

Verbal memory and executive function impairments are common in remitted patients with bipolar disorder (BD). We recently found that Action-Based Cognitive Remediation (ABCR) may improve executive function and verbal memory in BD. Here, we investigated neuronal changes associated with ABCR treatment-related memory improvement in a longitudinal functional MRI (fMRI) study. Forty-five patients with remitted BD (ABCR: \textit{n} = 26, control treatment: \textit{n} = 19) completed a picture-encoding task during fMRI and tests of verbal memory and executive function outside the scanner before and after two weeks of ABCR/control treatment. The cognitive assessment was performed again following ten weeks of treatment. Thirty-four healthy controls underwent the same test protocol once for baseline comparisons. Patients showed a moderate improvement in a domain composite of verbal learning and memory both after two weeks and ten weeks of ABCR treatment, which correlated with improved executive function. At baseline, patients showed encoding-related hypoactivity in dorsal prefrontal cortex compared to healthy controls. However, treatment was not associated with significant task-related neuronal activity changes. Improved verbal learning and memory may have occurred through strengthened strategic processing targeted by ABCR. However, picture-encoding paradigms may be suboptimal to capture the neural correlates of this improvement, possibly by failing to engage strategic encoding processes.

1. Introduction

Objective cognitive impairments across several domains are present in bipolar disorder (BD), even in remitted or subsyndromal patients (Bourne et al., 2013). Cognitive impairments in BD impede psychosocial function, occupational status, and quality of life (Baune and Malhi, 2015; Brissos et al., 2008; Tse et al., 2014). Specifically, verbal learning and memory has been identified as a robust indicator of neuropsychological impairment in BD and is associated with a significant impact on daily functioning and occupational outcome (Bonnín et al., 2012, 2010; Tse et al., 2014). Currently, no treatment for cognitive impairments in BD has shown replicable and enduring pro-cognitive efficacy (Kamilla W. Miskowiak et al., 2016a), although emerging evidence points to beneficial effects of cognitive remediation interventions (Lewandowski et al., 2017; Strawbridge et al., 2021). A study of functional remediation in BD revealed a selective improvement in verbal memory, which was associated with improved functioning at six months (Bonnín et al., 2016) and two years after treatment completion (Sole et al., 2020). Verbal memory thus seems particularly important for patients’ daily life functioning.

In line with the recommendations from the International Society for Bipolar Disorder (ISBD) Cognition Task Force (Miskowiak et al., 2017),
we recently conducted a double-blinded randomized controlled study of the effects of 10 weeks of group-based biweekly Action-Based Cognitive Remediation (ABCR) compared with weekly unstructured group sessions in remitted BD patients with cognitive impairments (for full study protocol see Ott et al., 2018; Ott et al., 2019). Specifically, ABCR involved a combination of strategic cognitive training and practical exercises to promote cognitive flexibility (Bowie et al., 2017). The study further included functional MRI (fMRI) assessments at baseline and after two weeks of treatment to explore early neuronal underpinnings of treatment-related changes in cognitive function. In line with the emphasis on strategy use and planning to solve cognitive challenges in ABCR, we found an improvement in executive function, the secondary trial outcome, as well as on tertiary measures of verbal learning and memory (Ott et al., 2020). The improvement of these two aspects of cognition - in the absence of changes in other domains - is interesting in light of evidence for an influence of executive functions on strategic aspects of verbal encoding and recall (Chang et al., 2010; Taconnet et al., 2010; Tremoni et al., 2000). The ABCR-related executive function improvements were accompanied and predicted by early increase in dorsal prefrontal cortex (dPFC) activity during a spatial working memory (WM) fMRI paradigm (Ott et al., 2021). However, the neuronal correlates of treatment-related improvements in verbal learning and memory are unclear. There is a paucity of studies investigating the neuronal correlates of memory impairments in mood disorders and the findings from these studies are conflicting (Miskowiak and Petersen, 2019). Using an episodic memory encoding paradigm that probes a network of medial temporal, parietal and prefrontal regions, we found that cognitively impaired vs. cognitively intact BD patients display reduced encoding-related activity in the middle temporal lobe but no differential dPFC or hippocampal response (Petersen et al., 2021). We also used this encoding paradigm to investigate the neuronal underpinnings of verbal memory improvement following treatment with the multifunctional growth factor erythropoietin (EPO) in patients with mood disorders (Miskowiak et al., 2016b). This revealed treatment-related dPFC and temporo-parietal activity increase, which correlated with patients’ memory improvement (Miskowiak et al., 2016b).

In the present longitudinal fMRI study, which was part of the above-mentioned ABCR trial (Ott et al., 2018), we employed the same episodic memory encoding paradigm to investigate whether this psychological intervention for cognitive impairments would produce similar changes in the neuromucularity target engagement as following EPO intervention. We hypothesized that improvement in verbal memory in ABCR vs. control groups would be accompanied by early changes in neuronal activity during episodic memory encoding after two weeks of treatment within (i) the medial temporal region showing aberrant encoding-related activity in cognitively impaired BD patients (Petersen et al., 2021) and (ii) the dPFC, reflecting strengthened strategic encoding processes dependent on executive functions, in line with the effects of ABCR on strategic aspects of cognition.

2. Methods

2.1. Procedure, randomisation and masking

Data were collected at the Psychiatric center Copenhagen, Rigshospitalet as part of the ABCR trial (Ott et al., 2018; Ott et al., 2019). An fMRI scan and assessments of verbal memory were carried out at baseline and week 3 following the completion of two weeks of treatment. Verbal memory was assessed again at treatment completion (week 10). In this outcome-assessor blind trial, participants were randomized to the ABCR or the control treatment in a 1:1 allocation order. We used allocation envelopes provided by Pharma Consulting Group (Uppsala, Sweden), and these were kept in a locked filing cabinet to prevent unblinding. Randomization was stratified by gender (female or male) and age (< or ≥35 years) due to the association between age and neuroplasticy (Park and Bischof, 2013). Upon inclusion, the primary therapist (CO) opened the randomization envelopes in a consecutive manner. For a power calculation for the primary outcome of the study, see the full protocol (Ott et al., 2018). Randomization was carried out from July 2017 to April 2019, and data collection was completed in January 2020.

2.2. Participants

Participants were recruited from psychiatric outpatient clinics and consultant psychiatrists in the Capital Region of Denmark. Inclusion criteria were: an ICD-10 diagnosis of BD confirmed in a semi-structured clinical interview using the Schedules of Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) in full or partial remission (full remission: ≤7, partial remission: 8–14 on the Hamilton Depression Rating Scale – 17 items (HDRS-17) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1976), respectively), in line with the recommendations from the International Society for Bipolar Disorder (ISBD). Cognition Task Force (Miskowiak et al., 2017), fluent in Danish, age between 18 and 55 years old, and objective cognitive impairment (total scores ≤74 or below the cut-offs on >2 subscales on the Screen for Cognitive Impairment in Psychiatry (SCIP) (Jensen et al., 2015)). Exclusion criteria were: daily use of benzodiazepines (>22.5 mg), current drug or alcohol abuse, neurological illness or previous severe head trauma, schizophrenia or a schizoaffective disorder, severe somatic illness, electroconvulsive treatment within the previous three months, dyslexia, pregnancy, pacemaker or other internal metal objects. Data from 34 healthy controls (HC) with no personal or first-degree family history of psychiatric illness from the ongoing Bipolar Illness Onset (BIO) study (Kessing et al., 2017) were included to assess whether a treatment-related neuronal change in ABCR vs. control treatment was towards normalization (i.e. HC activation levels). Data from the same HC sample were included to standardize the performance of the patient sample on neuropsychological tests of verbal learning and memory. Participants were informed about the study procedures and written consent was obtained. The study was approved by the local ethics committee (H-16,043,480) and the Danish Data Protection Agency (2012–58–0004).

2.3. Treatment and control groups

The ABCR program is a manual-based cognitive remediation treatment that provides an action-based top-down approach to restoration of cognitive impairment (Bowie et al., 2017). Treatment duration was 10 weeks with two-hour sessions twice a week and daily computer training at home. There were four to six patients in each group session, which included computerized training on the Danish version of Happy Neuron Pro (www.happyneuronpro.com/en), cognitive strategy learning, visual and verbal working memory, attention, memory and executive functions with application in practical activities (e.g., preparing a meal, updating one’s calendar etc.). Each session also included goal setting discussions to encourage participation in cognitively stimulating activities during daily life. In addition to the group sessions, participants were instructed to perform the computerized training program for 30 min every day at home. The control arm involved 10 weeks of weekly one-hour unstructured group sessions in which themes relevant to patients were discussed but did not entail any cognitive training (for more details, see Ott et al., 2018; Ott et al., 2019).

2.4. Neuropsychological assessment

The participants performed a range of neurocognitive tests described in Ott et al. (2020). Verbal learning and memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) consisting of the following subtests: RAVLT total recall lists I-V, RAVLT distractor list, RAVLT immediate recall, RAVLT delayed recall, and RAVLT recognition (Poreh,
Alternate, matched forms of the RAVLT were used at each assessment to minimize effects of learning. Executive functions were assessed using the following tests: RBANS Digit Span (Randolph et al., 1998), Spatial Working Memory task ‘between errors’ and ‘strategy’ measures from the CANTAB (Goldberg, 2013), Trail Making Test B (TMT B) (Adjudant General’s Office, 1944), verbal fluency letters “S” and “D” (Borkowski et al., 1967), and WAIS-III Letter-Number Sequencing (Wechsler, 1997).

2.5. Picture encoding fMRI task

The fMRI paradigm was programmed in e-prime 2.0 (Psychological Software Tools, Pittsburgh, PA, USA) and displayed on a screen which participants viewed using an angled mirror. The paradigm was based on the picture encoding task from Hariri et al. (2003) and identical to the one applied in our previous fMRI study (Miskowiak et al., 2016b). Participants were instructed to classify whether pictures showed ‘indoor’ or ‘outdoor’ scenes and to pay attention as they would be asked to recall the pictures, process involving memory encoding and executive functions. This was followed by a free recall test immediately after the scan. Pictures were matched for valence, arousal, and complexity and were presented in a blocked paradigm to maximize sensitivity for BOLD signal change (Birn et al., 2002). Six picture blocks (24 s each) were preceded by an instruction screen (2 s) and interleaved with a fixation cross (24 s), resulting in a task duration of 4 min and 50 s. Blocks consisted of six pictures presented serially for 3 s interleaved with a 1 s fixation cross. Each block contained an equal number of pictures representing indoor and outdoor scenes. Alternate, matched versions of the task were administered at baseline and follow-up in a counterbalanced order to minimize learning effects.

2.6. The fMRI analysis

2.6.1. MRI acquisition protocol

MRI data were obtained at the Copenhagen University Hospital, Rigshospitalet using a 3 Tesla Siemens Prisma scanner and a 64-channel head-coil. During the performance of the picture encoding task, blood oxygen level dependent (BOLD) fMRI was acquired using a T2*-weighted gradient echo spiral echo-planar (EPI) sequence with an echo time (TE) of 30 ms, repetition time (TR) of 2 s, and flip angle of 90°. A total of 146 vol were acquired, each consisting of 32 slices with a slice thickness of 3 mm with 25% gaps in-between, and a field of view (FOV) of 230 × 230 mm using a 64 × 64 grid. The BOLD images were registered to T1-weighted structural images (TR = 1900 ms; TE = 2.58 ms; flip angle = 9°; distance factor = 50%; FOV = 230 × 230 mm; slice thickness = 0.9 mm). A standard B0 field map sequence was also acquired with the same FOV and resolution as the fMRI sequence (TR = 400 ms; TE = 7.38 ms; flip angle = 60°) and used for geometric distortion correction of the BOLD images. The image quality was ascertained by visual inspection of all individual images.

2.6.2. Data pre-processing and subject-level analysis

Functional MRI data processing was performed with the FMRI Expert Analysis Tool (FEAT; version 6.01) part of FMRIB’s Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Pre-processing involved image B0 field distortion correction with acquired field map image, realignment of the acquired volumes, non-brain removal, spatial normalization to a Montreal Neurologic Institute (MNI) template, and spatially smoothing (Gaussian kernel, 5 mm full-width-half-maximum). The time series in each session were high pass-filtered (max 0.02 Hz). At subject level, we modelled the picture encoding task using a block design, with the picture presentation (i.e., memory encoding) and fixation cross as events that were convolved with a double-gamma hemodynamic response function and added temporal derivatives for improved fit to the data.

2.6.3. Group-level analyses

At the group level, we first estimated task activations at baseline for the HC group by entering the picture encoding contrast at baseline in a one-sample t-test. Secondly, we estimated group-by-time interaction effects for picture encoding responses using a two-way mixed effect repeated measures ANOVA model (group factor: ABCR vs. control, time factor: baseline and follow-up). The significance level for clusters was set at p < 0.05 corrected for multiple comparisons using Gaussian Random Field (GRF) theory subsequent a cluster-forming threshold of z = 2.57 (p < 0.005). The models were estimated twice, first restricting the search volume to the dPFC and secondly at whole brain level.

For the ROI analysis, we extracted the mean percent BOLD signal change from a right dPFC, left MTG, and the hippocampi ROIs in all participants. Using two-sample t-tests we first compared HC and BD participants at baseline in all ROIs. We secondly estimated the longitudinal effect of ABCR treatment vs. control in BD patients using a repeated measures general linear model implemented in SPSS v25 (IBM, Armonk, New York, United States).

2.7. Statistical analyses of behavioral data

A cognitive domain composite score of ‘verbal learning and memory’ were created by standardizing and averaging the following RAVLT subtests: RAVLT total recall lists I-V, RAVLT immediate recall, RAVLT delayed recall, and RAVLT recognition based on the mean and standard deviations (SD) of the HC group. Verbal learning and memory composite scores were created for the baseline scores, two weeks of treatment scores, and the treatment completion scores. A similar procedure was used for calculation of the ‘executive function’ composite score, which was used for a post-hoc analysis of the association between changes in the ‘verbal learning and memory’ and ‘executive function’ domains; for details see Miskowiak et al. (2021).

To assess the effect of ABCR vs. control treatment on verbal learning and memory, we conducted linear mixed-effect models. Factors were time, stratum (classifying age and gender), and treatment (control treatment as reference category). Fixed effects were time, stratum, time*stratum, and time*treatment. Baseline correction was applied.

To assess the association between changes in ‘verbal learning and memory’ and ‘executive function’ (a key target for ABCR), we conducted a multiple regression analysis with adjustments for demographic and clinical variables (age, gender, years of education, verbal IQ, and change in HDRS-17 and YMRS scores, respectively).

Finally, performance on the picture encoding task outside the scanner (total recall and false recall) was assessed with repeated measures analyses of variance (ANOVA) with time as the within-subjects variables and group at the between-subjects factor. Behavioural data was analysed in SPSS at the α-level = 0.05.
3. Results

3.1. Participants

Among the patients included in the ABCR trial (ABCR: \( n = 32 \), control: \( n = 29 \)), fMRI data were complete and analyzed for \( n = 45 \) patients; \( n = 26 \) (81%) in the ABCR group and \( n = 19 \) (66%) in the control group (see Fig. 1 for CONSORT flow diagram). There were no significant clinical or demographic differences between patients with complete fMRI data (\( n = 45 \)) and patients without fMRI data (\( n = 16 \)) in age, gender, years of education, verbal IQ, mood symptoms, mood episodes, illness duration, hospitalizations, and BD type (\( p s \geq 0.23 \)). There was no significant between-group difference in the time from the fMRI scanning at baseline to after two weeks of treatment (ABCR: Mdn = 21.5 days, interquartile range = 2; control: Mdn = 21.0, interquartile range = 2, \( U = 207, p = 0.34 \)). The demographic and clinical data in the ABCR and control groups were well-balanced, although more patients in the control group took antidepressants (\( p = 0.02 \)) (Table 1).

Patients in the trial had more subsyndromal mood symptoms and fewer years of education compared to the HC sample included for baseline verbal memory and fMRI comparisons (\( ps \leq 0.01 \)) (Table 2).

3.2. Behavioral results

Remitted BD patients showed deficits in the domain of verbal learning and memory at baseline with a large effect size (\( t(77) = -5.6, 95\% \text{ CI } [-2.68, -1.28], p < 0.001, \text{ Cohen's } d = 1.32 \)). There was a significant effect of ACBR vs. control treatment on the verbal learning
controls.

lower total recall ($F = 2.705, p = 0.023, \eta^2_p = 0.70$). There was no difference between the ABCR and the control BD patients on the picture recall ($M_{\text{score}} = 32.8$, $t = 1.87, p = 0.08, \text{effect size} = 0.54$).

The post-scan picture recall test showed a lower performance at baseline for the BD patients compared to the HC participants with a $t$-test ($t = -2.70, p = 0.01, \eta^2_p = 0.54$). There was no significant difference between ABCR and control BD patients on the picture recall ($t = -1.58, p = 0.12, \text{effect size} = 0.38$).

The voxel-wise analyses showed no significant differences between the HC and BD groups at baseline within the dPFC mask and at whole brain. However, the ROI analysis showed dPFC hypoactivity in BD compared to HC in the dPFC ROI ($F(1,77) = 5.695, p = 0.019, \eta^2_p = 0.069$) and the paracingulate cluster activated in the HC group ($F(1,77) = 8.030, p = 0.006, \eta^2_p = 0.094$). No significant group difference was observed in the hippocampi or the MTG ROIs ($p > 0.195$).

There were no significant differential longitudinal changes in neuronal response to episodic memory encoding (group-by-time interaction effects) between the ABCR and control BD patients within the dPFC mask or at whole brain. Similarly, the ROI analyses of the extracted BOLD signal change showed no group-by-time interaction effects in any of the tested ROIs ($p > 0.54$, Fig. S).

4. Discussion

This is the first randomized controlled fMRI study to investigate the neuronal correlates of improved verbal learning and memory in remitted BD patients following ABCR treatment. In this subgroup of 45 patients with complete longitudinal fMRI data, we confirmed our previous preliminary report on treatment-related improvements in verbal learning and memory for ABCR vs. control treatment, which emerged already after two weeks of treatment. Specifically, ABCR-treated patients showed improvement in a domain composite score of verbal learning and memory, which correlated directly with increase in executive functions. At a neural level, patients showed encoding-related dPFC hypoactivity relative to HC. However, in contrast with the hypotheses, we observed no early encoding-related neuronal activity change in the dPFC, hippocampus or MTL after ABCR vs. control treatment.

The absence of differential neuronal activity changes between ABCR and control treatment contrasts with our previous findings of increased ABCR-related dPFC activity during working memory in the same sample of patients (Ott et al., 2021). This change in prefrontal activity was interpreted as a treatment-related modulation of dorsal neuronal resources during executive performance. Given our preliminary findings of potential effects of ABCR on executive functions and the importance of executive functions in strategic aspects of verbal memory, we had hypothesized that we would observe similar activity in the dorsal prefrontal area in addition to change in MTI activity using the picture encoding task. The absence of such neuronal changes was therefore surprising and could suggest that patients did not employ strategic learning in the applied picture encoding paradigm as expected. Indeed, examining the task-related activations at baseline did not show expected prefrontal engagement in our patient cohort. While the HC displayed encoding-related dorsomedial PFC activation (Fig. S), patients showed hypoactivity in this prefrontal region. This absence of encoding-related prefrontal activity in patients suggests that they failed to implement strategic encoding strategies, which may also explain their poorer recall performance compared to HC after the scan. Our findings also contrast with the previous study of erythropoietin (EPO) in which we found treatment-related increase in dPFC and tempo-parietal regions during picture encoding, which correlated with improvement in post-scan picture recall (Mikolowski et al., 2016b). These differences in the neuronal activity after EPO and ABCR interventions could reflect the distinct mechanisms of these treatments. Specifically, neuroplasticity increase with EPO treatment may account for the more global changes in cognition-relevant cortical networks, including the dPFC, parietal and temporal regions as well as hippocampal volume and function.
Fig. 2. Behavioral performance for the picture encoding post-scan recall in the Action-Based Cognitive Remediation (ABCR) and Control bipolar patient groups, and healthy controls (HC). Error bars represent standard error of the mean. Data from 5 HC is missing.

Fig. 3. Neuronal response to picture encoding in the Action-Based Cognitive Remediation (ABCR) and Control bipolar patient groups, and healthy controls (HC). Top panel – statistical map showing task activations at baseline in HC together with investigated regions-of-interest (green). Bottom panels - bar charts displaying neuronal response extracted from the regions-of-interest (ROIs) in ABCR (red), control treatment (blue), and HC (green) participants. Error bars represent standard error of the mean.
(Miskowiak et al., 2016b; Miskowiak et al., 2015). In contrast, ABR
seems to primarily increase executive functions and associated dPFC activity (Ott et al., 2021), which was a key focus in the interventions and is likely to mediate the observed improvement in verbal memory. Indeed, we observed a direct correlation between changes in verbal memory and executive functions in our participants after controlling for demographic and clinical variables. This association is in line with evidence for an impact of executive functions on strategic aspects of verbal learning and memory, especially in encoding and recall tasks (Chang et al., 2010; Hill et al., 2012).

This present report has implications for future cognition trials in BD. Based on the current findings, an episodic memory encoding fMRI paradigm may not be sensitive to capture treatment-related neuronal activity following ABR in BD patients. This is in line with our previous report in which we observed no underlying activity difference in cognitively impaired vs. intact BD patients using the same picture encoding task (Petersen et al., 2021). In addition, the encoding paradigm did not show sensitivity towards change in activity due to the occurrence of mood episodes. The present findings add to this emerging evidence indicating that this fMRI paradigm does not capture the neuronal correlates of episodic memory improvements. In contrast, WM tasks seem more sensitive to detect underlying neuronal changes of treatment-related improvement in cognition following ABR (Ott et al., 2021). We therefore recommend that future cognition trials in mood disorders implement fMRI paradigms that are more focused on the cognitive domain that shows treatment-related improvement to examine neurocircuitry target engagement.

Strengths of the present study were that it followed the recommendations from the ISBD Cognition Task Force regarding inclusion of remitted patients with objective cognitive impairments and investigation of underlying neuronal activity in relation to the patient’s outside scanner cognitive performances (Miskowiak et al., 2017). Since significant levels of subsyndromal symptoms were allowed in patients within our trial, the findings may not be representative of patients in full remission. However, ABR and control groups showed no differential change in subsyndromal symptoms over time (Ott et al., 2020), suggesting that the present findings were not confounded by unspecific effects of mood. A limitation of the current study was that we used an fMRI paradigm that probes visual memory for investigating the neuronal correlates of verbal memory improvement. Nevertheless, both the verbal learning and memory (RAVLT) and picture encoding tests probe episodic memory processes that involve strategic processes and the integrity of overlapping fronto-temporal regions (Kim, 2011). In addition, all participants in the patient group received psychopharmacological treatment which may have influenced their neuronal response (e.g., in the hippocampus). However, this does not explain the absence of changes in encoding related neuronal activity given the previous observation of dorsal prefrontal activity change following ABR treatment in the same cohort (Ott et al., 2021). Another limitation was the significant increase in post-scan picture recall from baseline to follow-up in both patient groups which suggests a learning effect which may have precluded ABR-related treatment effects. Lastly, verbal learning and memory was only a tertiary outcome in the original ACBR trial (Ott et al., 2020) and the findings should therefore be considered exploratory. Nevertheless, our calculation of an overall domain composite score for verbal learning and memory in the present report revealed robust treatment-related change in this measure, which emerged already after two weeks of treatment and had a large effect size after treatment completion.

In the present fMRI study, we investigated the neuronal correlates of verbal learning and memory improvement following 10 weeks of ABR in remitted patients with BD. We showed ABR-related improvement in an overall measure of verbal learning and memory after two and 10 weeks of treatment. This effect correlated directly with improved executive functions and was likely mediated by strengthened strategic processing – a key focus in ABR. Nevertheless, neuronal activity during picture encoding was not affected by ABR. We suggest that picture encoding paradigms that do not explicitly tap into strategic cognitive processes may be suboptimal for capturing the neuronal underpinnings of memory improvement following cognitive remediation interventions in BD.

Contributors

KWM, VD and CVO planned and conducted the behavioral analyses. JM conducted the fMRI analyses. VD and KWM created the first draft of the manuscript, which was then revised by JM. GMK and LVK were involved in the original trial design together with KWM. All authors reviewed and approved the final version of the manuscript.

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Declaration of Competing Interest

The authors declare no potential conflicts of interest with respect to this work. KWM declare to have received consultancy fees from Lundbeck and Janssen-Cilag in the past three years.

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