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Research paper

Longitudinal changes in neurometabolite concentrations in the dorsal anterior cingulate cortex after concentrated exposure therapy for obsessive-compulsive disorder

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ABSTRACT

Background: The dorsal anterior cingulate cortex (dACC) plays an important role in the pathophysiology of obsessive-compulsive disorder (OCD) due to its role in error processing, cognitive control and emotion regulation. OCD patients have shown altered concentrations in neurometabolites in the dACC, particularly Glx (glutamate+glutamine) and tNAA (N-acetylaspartate+*N*-acetyl-aspartyl-glutamate). We investigated the immediate and prolonged effects of exposure and response prevention (ERP) on these neurometabolites.

Methods: Glx and tNAA concentrations were measured using magnetic resonance spectroscopy (1H-MRS) in 24 OCD patients and 23 healthy controls at baseline. Patients received concentrated ERP over four days. A subset was re-scanned after one week and three months.

Results: No Glx and tNAA abnormalities were observed in OCD patients compared to healthy controls before treatment or over time. Patients with childhood or adult onset differed in the change over time in tNAA ($F(2,40) = 7.24$, $\eta^2_p = 0.27$, $p = 0.004$): concentrations increased between one week after treatment and follow-up in the childhood onset group ($t(39) = -2.43$, $d = -0.86$, $p = 0.020$), whereas tNAA concentrations decreased between baseline and follow-up in patients with an adult onset ($t(42) = 2.78$, $d = 1.07$, $p = 0.008$). In OCD patients with versus without comorbid mood disorders, lower Glx concentrations were detected at baseline ($t(38) = -2.28$, $d = -1.00$, $p = 0.028$). Glx increased after one week of treatment within OCD patients with comorbid mood disorders ($t(30) = -3.09$, $d = -1.21$, $p = 0.004$).

Limitations: Our OCD sample size allowed the detection of moderate to large effect sizes only.

Conclusion: ERP induced changes in neurometabolites in OCD seem to be dependent on mood disorder comorbidity and disease stage rather than OCD itself.

1. Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by obsessions (intrusive, persistent thoughts) and compulsions (repetitive and excessive/unrealistic ritualistic behaviors) (Stein et al., 2019). OCD is associated with abnormal function within and between the parallel cortico-striato-thalamo-cortical, fronto-parietal and fronto-limbic circuits (Pauls et al., 2014; Stein et al., 2019; van den Heuvel et al., 2016). Within these circuits the dorsal anterior cingulate cortex (dACC) serves an important role in cognitive control,

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action monitoring, emotion regulation, and conflict processing. Aberrant dACC functioning could therefore result in cognitive inflexibility and difficulty stopping obsessive thoughts and compulsive behaviors in OCD (Maltby et al., 2005; Marsh et al., 2014; McGovern and Sheth, 2017; Thorsen et al., 2018). Indeed, the dACC has been implicated in OCD using both functional and structural neuroimaging, showing hyperactivity in the dACC of OCD patients during functional magnetic resonance imaging (fMRI) using cognitive and emotional paradigms, resting-state fMRI, and positron emission tomography (Cheng et al., 2013; Fitzgerald et al., 2005; McGovern and Sheth, 2017; Pico-Perez et al., 2020; van den Heuvel et al., 2005). Additionally, the dACC of OCD patients is shown to have a lower gray matter volume and a thinner cortex (Goodkind et al., 2015; Radua et al., 2010).

Using proton magnetic resonance spectroscopy (1H-MRS), regional abnormalities in neurometabolite concentrations have also been reported in OCD patients, although results are mixed (see (Vester et al., 2020) for a review). Glutamate, the most important excitatory neurotransmitter in the brain (Petroff, 2002), plays an important role in the balance between the direct and indirect pathways of the parallel CSTC circuits involved in emotional and cognitive processes underlying the symptoms in OCD (Pittenger et al., 2011; Stein et al., 2019). The role of glutamate in OCD is also supported by genome-wide linkage studies and candidate gene association studies showing possible relations between OCD and genes encoding for postsynaptic glutamate transporters or glutamate receptor subunits (Bloch and Pittenger, 2010; Pittenger, 2015).

Both higher (Naaijen et al., 2017) and lower (Rosenberg et al., 2004) Glx (sum of glutamate and glutamine) concentrations have been reported in the dACC of pediatric OCD patients compared to healthy controls. In adult OCD, one study found lower Glx concentrations in the dACC of female patients (Yucel et al., 2008), whereas most studies did not find abnormal glutamate or Glx concentrations in the dACC of adult OCD patients in comparison with healthy controls (Bedard and Chantal, 2011; Fan et al., 2017; O'Neill et al., 2016; Starck et al., 2008; Vester et al., 2020; Wang et al., 2017; Zhang et al., 2016). Previous research has also investigated N-acetylaspartate (NAA) and total NAA (tNAA; a combination of NAA and N-acetyl-aspartyl-glutamate) concentrations in OCD patients. Although its role in OCD is less clear, lower tNAA concentrations are thought to reflect less neuronal integrity and viability (Aoki et al., 2012; Moffett et al., 2014). Multiple studies detected lower NAA and tNAA concentrations in the (d)ACC of OCD patients compared to controls (Gnanavel et al., 2014; Jang et al., 2006; O'Neill et al., 2013; Tukel et al., 2014). A meta-analysis by Aioki et al. showed a negative relation between NAA levels in the medial prefrontal cortex of OCD patients and symptom severity (Aoki et al., 2012).

Cognitive behavioral therapy (CBT) with exposure and response prevention (ERP) is an effective treatment strategy for OCD (Ost et al., 2015), even when delivered in a very short time period, such as over four consecutive days in the Bergen 4-Day Treatment format (B4DT) (Hansen et al., 2018, 2019; Havnen et al., 2017; Launes et al., 2019). Studies on the effects of CBT on neurometabolite concentrations in OCD patients have not provided consistent results (Vester et al., 2020). Some found decreases in Glx in the left dACC of adult OCD patients after intensive CBT (O'Neill et al., 2013) or in the pregenual ACC of pediatric patients after three months of CBT (O'Neill et al., 2017), while others showed CBT-induced increases in tNAA in the caudate nucleus (Whiteside et al., 2012) or right pregenual ACC (O'Neill et al., 2013). However, this was not found in the rostral ACC (Zurowski et al., 2012). Inconsistent findings on the effects of CBT on neurometabolites might be explained by factors such as medication status (O'Neill et al., 2016; Yucel et al., 2007), comorbid depression or anxiety disorders (Bedard and Chantal, 2011; Fan et al., 2017), age, age at OCD onset or disease duration (Ortiz et al., 2015), or the amount of time between pre- and post-treatment imaging.

The current study aimed to investigate both immediate and prolonged effects of concentrated ERP on neurometabolite concentrations in the dACC of patients with OCD. As described in our preregistered analysis plan at the Open Science Framework (https://osf.io/w34rn/), we expected that Glx concentrations in OCD patients would be similar to controls at baseline, while tNAA concentrations would be lower in OCD patients. We also expected, in line with previous literature, a treatment-induced reduction in Glx concentrations, with a further decrease after three months. Regarding tNAA, we expected to see an increase in tNAA concentration in OCD patients after treatment. As tNAA is thought to reflect slow processes such as changes in neuronal viability and plasticity (Moffett et al., 2014), we expected to see this change mainly at three months follow-up. Furthermore, we hypothesized that treatment-induced changes in both Glx and tNAA would be related to changes in symptom severity after treatment. Regarding age at disease onset, we expected to see lower tNAA at baseline and less clinical response to treatment in the childhood onset group (Jakubovski et al., 2013). In exploratory analyses, we investigated the effects of medication status and comorbidity.

2. Materials and methods

2.1. Participants

Thirty-three (33) OCD patients (12 males, 21 females; age: 30.3 ± 8.9 years) were recruited from the Haukeland University Hospital in Bergen, Norway. All patients received the B4DT by the OCD team as part of the standard public health care (see below). Also, 31 healthy control participants (12 males, 19 females; age: 30.9 ± 10.4 years) were included from the surrounding community. OCD patients and healthy controls were matched according to sex, handedness, age, and years of education (table S1 for full sample demographics). Patients were included if they were diagnosed with OCD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-4-TR) according to the Structured Clinical Interview for DSM-4 (SCID-IV) (First et al., 2002), and scored ≥16 on the Yale-Brown Obsessive Compulsive scale (Y-BOCS) (Goodman et al., 1989). Exclusion criteria were predominant hoarding symptoms, substance dependence, bipolar disorder or psychosis, suicidal ideation, mental retardation, and unwillingness to refrain from alcohol and benzodiazepines during the treatment. Healthy control participants had no lifetime history of a mental disorder according to the SCID-IV. All patients had to be between 18 and 65 years old and had to be fluent in Norwegian. Participants were excluded if they had any contraindications for MRI. The study was approved by the Regional Ethics Committee for South-Eastern Norway and all participants provided written informed consent before participating in accordance with the declaration of Helsinki.

2.2. Bergen 4-Day treatment

Groups of 3–6 OCD patients received the B4DT over four consecutive days (Havnen et al., 2014). Day 1 consisted of a three-hour group session with psychoeducation and planning exposure tasks. Day 2–3 consisted of therapist-assisted ERP with a 1:1 ratio of patients and therapists for 8–10 h a day. Relatives and friends were also invited to attend a lecture on OCD and the therapy. Day 4 focused on summarizing the treatment and relapse prevention, along with planning self-exposure for the next three weeks. After three months, the patients participated in a follow-up session summarizing their progress and future plans (See (Launes et al., 2019) for details).

2.3. Clinical assessments

Independent clinical assessments were obtained at all three time points. Symptom severity of OCD was measured using the Y-BOCS at baseline, directly after treatment, and at follow-up. Response to treatment was defined by a minimum reduction of 35% in Y-BOCS score, whereas patients were considered in remission when they also scored

≤12 (Mataix-Cols et al., 2016). Both the OCD patients and healthy controls filled out the Obsessive Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002) as a self-report measure of OCD symptom severity, the Patient Health questionnaire 9 (PHQ-9) (Kroenke et al., 2001) for depressive symptoms, and the Generalized Anxiety disorder 7 (GAD-7) (Spitzer et al., 2006) for symptoms of anxiety.

The presence of mood and anxiety comorbidity were defined using the SCID-IV. Patients with either comorbid major depressive disorder or dysthymia were grouped together in the mood comorbidity group (regardless of comorbid anxiety disorders). While patients with comorbid social anxiety disorder and or, generalized anxiety disorder, specific phobia, panic disorder, agoraphobia, posttraumatic stress disorder were grouped together in the anxiety group (regardless of comorbid mood disorders). For analyses related to OCD onset, we relied on retrospective self-reports of onset which were dichotomized to adult (>18 years) or childhood (<18 years) onset groups.

2.4. MR acquisition

All MRI scans were performed on a 3T General Electric Discovery MR750 (GE Healthcare, Milwaukee, Wisconsin, USA) using an eight-channel head coil. The scanning protocol included a whole-brain structural T1-weighted image for brain tissue segmentation and the individual localization of the MRS voxel in each participant. The T1-weighted image was acquired using a 256×256 matrix, 192 slices, isotropic voxel size=1mm^3, echo time (TE) = 3000 ms, repetition time (TR) = 7000 ms, flip angle=12°, field of view (FoV) = 256 mm. Single voxel MRS was obtained using a point resolved spectroscopy (PRESS) sequence (TR=1500 ms, TE=35 ms, number of averages=128, voxel size (RLxAPxSI) = 16×24×20 mm^3, number of data points=4096, bandwidth=5 kHz). The MRS voxel was placed parallel to the frontal part of the midline corpus callosum on the dACC by an experienced MRI radiographer, using placement in prior sessions as reference for the second and third scan (see Fig. 2A).

MRS scans were acquired the day before treatment (i.e. baseline; T0), three days directly after treatment (i.e. 1 week after baseline; T1) and three months post-treatment (T2). Subjective units of distress (SUDS) scores ranging from 0 to 100 were acquired directly after imaging.

2.5. Spectral quantification and quality control

1H-MRS spectra were fitted using Linear Combination Model (LCModel) version 6.3–0 L (Provencher, 2001) with the GE basis set. An example of a representative MRS spectrum is shown in Fig. 2B. After eddy current correction, water scaling was applied to estimate raw Glx and tNAA concentrations, as well as other neurometabolites including glutamate (Glu), glutamine (Gln), NAA, N-acetyl-aspartyl-glutamate (NAAG), creatine and phosphocreatine (Cr), choline-containing compounds (Cho), and myo-inositol (Ins) for exploratory analysis. We used FMRIB's Software Library (FSL) version 5.0.10 for preprocessing the structural scans (Jenkinson et al., 2012) that encompassed skull stripping (Smith, 2002) and tissue segmentation into gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) to perform partial volume correction using FSL FAST (Zhang et al., 2001). Raw neurometabolite concentrations were corrected for partial volume effects according to the LCModel guidelines (Provencher, 1993), and expressed in institutional units (IU).

The MRS spectra were fitted between 3.67 and 1.0 ppm to prevent influence of spoiling artefacts, while including the resonance of Ins. Spectra were excluded when at least one of the following criteria was met: full width half maximum (FWHM) ≥ 0.1 ppm, Cramer-Rao lower bounds of at least one of the main metabolites Glx, tNAA, Cr, Cho, and Ins were >20%, and the signal to noise ratio (SNR) < 14 (see flowchart in Fig. 1). Consistency of voxel placement was visually inspected at all time points by registering the structural scans and corresponding voxels to standard space (MNI) for each participant (Jenkinson et al., 2002; Jenkinson and Smith, 2001).

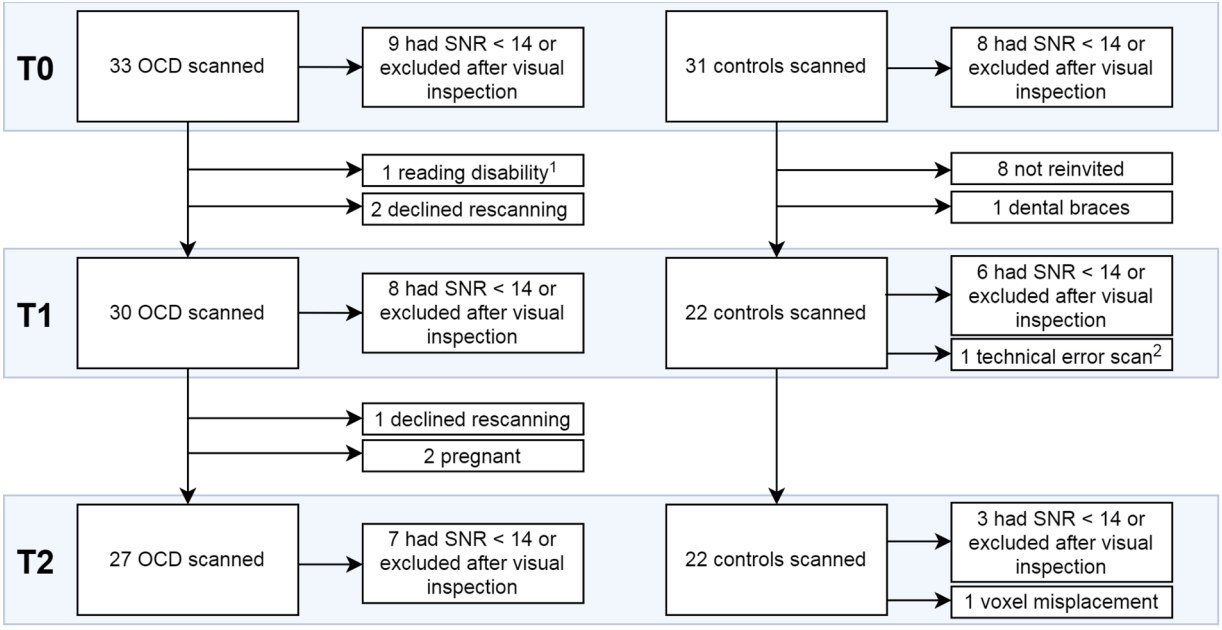

Fig. 1. Number of participants and reasons for exclusion are provided between each time point. Furthermore, quality of MRS spectra was assessed at every time point. MRS spectra were excluded when the signal to noise ratio was below 14, or after visual inspection. It is therefore possible that subjects that were included at T0 are not included at subsequent time points or vice versa. At baseline (T0), 33 OCD patients and 31 healthy controls were scanned. However, after applying spectral criteria, 24 patients and 23 controls were included for analyses at this time point. After one week (T1), 30 OCD patients and 22 controls were scanned but after quality assessment 22 patients and 15 healthy controls were included for analyses. Twenty-seven OCD patients and 22 controls were scanned at follow-up (T2), but 20 patients and 18 healthy controls were included for analyses. [1]Excluded due to reading disability that interfered with cognitive testing. [2]One control participant was excluded due to technical error at T1, but this participant was again included at T2.

2.6. Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics 22. Sex and handedness were compared between OCD patients and healthy controls using chi-squared tests. Group comparisons of age, years of education, and clinical variables were tested using independent t-tests at each time point. Differences in Glx and tNAA concentrations between OCD patients and healthy controls were also assessed at each time point using independent t-tests with False Discovery Rate (FDR) correction for multiple comparisons (α=0.05) (Benjamini and Hochberg, 1995).

A linear mixed model (LMM) design (with group and time as fixed effects and intercept for subjects as random effect) with FDR correction (α=0.05) was used for group by time analyses as this model allows for using all available data without imputation or listwise deletion, leading to increased power (Gallop and Tasca, 2009; Tasca and Gallop, 2009). Different covariance structures were used to take into account the correlation of neurometabolite concentrations between time points and to ensure best model fit (Littell et al., 2000). To do so, the variance across and correlation between time points was assessed and the best fitting appropriate covariance structure was selected based on the chi-squared likelihood ratio tests. We used a compound symmetry covariance structure for tNAA, and an AR(1) (autoregressive) structure for Glx analyses. These structures were used to investigate all tNAA and Glx effects over time, including analyses on medication, comorbidity, and age of onset. AR(1) structure was also used for exploratory analyses of Glu, Gln, NAA, NAAG, Cr, Cho and Ins. Medication status was a priori added to the model to assess its influence on the model fit. Post-hoc t-tests were performed on the estimated values when the main effect was significant after FDR correction. Therefore, we did not use additional multiple comparison corrections for these tests. LMMs with a scaled identity covariance structure were used to investigate the association between changes in metabolite levels and changes in clinical variables (i.e., Y-BOCS, PHQ-9, GAD-7 and OCI-R scores) over time in OCD patients. For OCD patients, we used exploratory correlational analyses to see whether Glx and tNAA concentrations were related to pre-treatment Y-BOCS, PHQ-9, GAD-7, and OCI-R scores.

3. Results

3.1. Demographics and clinical scores

After applying MRS quality criteria, the sample for MRS analyses consisted of 24 controls and 23 OCD patients at baseline (T0), including eight patients that were using medication (see Table 1). Medication status did not change during the time of the study. See the flowchart in Fig. 1 for exclusions and drop-out. For longitudinal MRS analyses data from 22 OCD patients and 15 controls were available at T1 and 20 OCD patients and 18 controls at T2.

The demographics and clinical characteristics of the full sample are described in table S1. At baseline there were no differences between OCD patients and healthy controls concerning age, sex, handedness, and years of education. OCD patients scored significantly higher on the PHQ-9, GAD-7, and OCI-R questionnaires at each time point. For the SUDS, OCD patients scored higher after treatment and at follow-up compared to control participants (Table S1). LMM analyses in OCD patients showed significant decreases over time on the PHQ-9 ($F(2,48) = 4.19$, partial eta-squared (η^2_p) = 0.15, $p = 0.021$), GAD-7 ($F(2,50) = 19.14$, $\eta^2_p = 0.43$, $p < 0.001$), and OCI-R ($F(2,48) = 33.29$, $\eta^2_p = 0.59$, $p < 0.001$) (see Table S2).

The clinical response to the B4DT showed that $n = 26$ (87%) responded, of whom $n = 18$ (60%) reached remission after four days of treatment. At three months follow-up, $n = 25$ (83%) were considered responders, of whom $n = 21$ (70% of all patients) maintained remission. Information of two patients was missing at this time point due to the fact that one patient dropped-out and one patient was unavailable for the Y-BOCS interview. The Y-BOCS showed a significant effect of time in the OCD patients ($F(2,61) = 137.53$, $\eta^2_p = 0.82$, $p < 0.001$). Post-hoc analyses revealed a significant decrease in Y-BOCS scores between T0 and T1 ($t(60) = -14.29$, Cohen's d (d) $= -5.61$, $p < 0.001$), whereas Y-BOCS

Table 1
Demographics and clinical characteristics of OCD patients and healthy control participants at baseline and overtime for the clinical measures for sample after spectral quality control.

Characteristic	OCD patients $N = 24$	Healthy controls $N = 23$	p
Age (mean years ± SD)	29.1 ± 8.4	29.7 ± 9.3	0.84[a]
Sex			
Female, *N* (%)	17 (71)	15 (65)	0.76[b]
Handedness			
Right, *N* (%)	23 (96)	21 (91)	0.48[b]
Years of education (mean ± SD)	14.4 ± 2.2	14.3 ± 2.3	0.82[a]
PHQ-9 (mean ± SD)			
T0	12.1 ± 6.2 (*N* = 22)	2.7 ± 1.7 (*N* = 22)	<0.001[a]
T1	9.1 ± 6.2 (*N* = 19)	2.6 ± 2.0 (*N* = 14)	<0.001[a]
T2	8.5 ± 5.9 (*N* = 15)	2.2 ± 1.6 (*N* = 17)	<0.001[a]
GAD-7 (mean ± SD)			
T0	12.7 ± 5.2 (*N* = 22)	2.8 ± 2.5 (*N* = 22)	<0.001[a]
T1	8.7 ± 5.1 (*N* = 19)	2.1 ± 2.0 (*N* = 14)	<0.001[a]
T2	6.9 ± 5.0 (*N* = 16)	1.9 ± 2.2 (*N* = 17)	<0.001[a]
OCI-R (mean ± SD)			
T0	26.2 ± 9.6 (*N* = 22)	6.9 ± 7.5 (*N* = 22)	<0.001[a]
T1	12.2 ± 8.5 (*N* = 19)	6.8 ± 8.5 (*N* = 14)	0.08[a]
T2	13.1 ± 9.9 (*N* = 15)	4.6 ± 5.9 (*N* = 17)	0.004[a]
SUDS (0–100) (mean ± SD)			
T0	15.0 ± 13.3 (*N* = 23)	12.0 ± 16.5 (*N* = 23)	0.5[a]
T1	20.0 ± 21.1 (*N* = 22)	8.1 ± 11.7 (*N* = 15)	0.035[a]
T2	13.9 ± 15.6 (*N* = 20)	4.0 ± 4.3 (*N* = 17)	0.013[a]
Y-BOCS (mean ± SD)			
T0	26.0 ± 4.0 (*N* = 24)	–	–
T1	10.7 ± 7.0 (*N* = 22)	–	–
T2	10.0 ± 6.7 (*N* = 20)	–	–
Comorbidities (at T0), *N* (%)			
Anxiety[c]	11 (46)	–	–
Mood[d]	8 (33)	–	–
ADHD	1 (4)	–	–
Somatization disorder	1 (4)	–	–
Pain disorder	1 (4)	–	–
Onset, *N* (%)			
Childhood onset	12 (50)	–	–
Adult onset	12 (50)	–	–
Medication use, *N* (%)			
SRI	6 (25)	–	–
SRI + antipsychotic	1 (4)	–	–
Methylphenidate	1 (4)	–	–

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; GAD-7, Generalized Anxiety disorder 7; OCI-R, Obsessive Compulsive Inventory-Revised; PHQ-9, Patient Health questionnaire 9; SRI, serotonin reuptake inhibitor; SUDS, Subjective Units of Distress Scale; T0, baseline; T1, directly after treatment; T2, three months after treatment; Y-BOCS, Yale-Brown Obsessive Compulsive scale.

[c] social anxiety disorder and or, generalized anxiety disorder, specific phobia, panic disorder, agoraphobia, posttraumatic stress disorder.

[d] major depressive disorder or dysthymia.

[a] Independent *t*-test.

[b] Fisher's Exact Test.

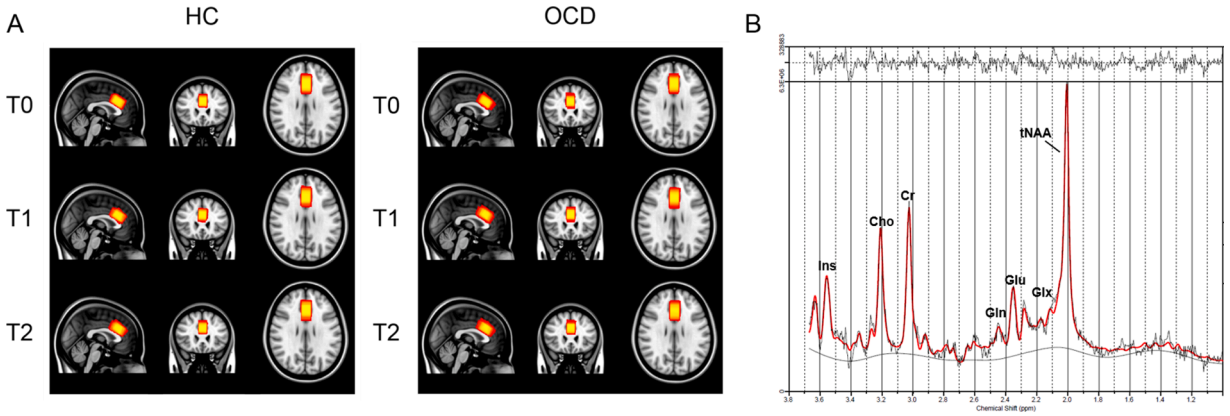

Fig. 2. (A) Placement of magnetic resonance spectroscopy (MRS) voxels on the dorsal anterior cingulate cortex (dACC), with yellow indicating greater overlap between participants. (B) Representative MRS spectrum fitted by LCModel with SNR = 20 and linewidth (FWHM) = 0.029 ppm. Neurometabolites include: Ins, myo-inositol; Cho, choline; Cr, creatine; Gln, glutamine; Glu, glutamate; NAAG, N-acetyl-aspartyl-glutamate; NAA, N-acetylaspartate. Glu and Gln are measured together as Glx, NAAG and NAA are measured together as tNAA.

scores did not change between T1 and T2 ($t(61) = -0.53$, Cohen's d (d) $= -0.22$, $p = 0.60$). No effect of medication, age of onset and anxiety comorbidity on Y-BOCS scores were seen. However, adding mood comorbidity to the model showed a significant effect of group ($F(1,32) = 5.50$, $\eta^2_p = 0.15$, $p = 0.025$), where patients with a comorbid mood disorder scored higher on the Y-BOCS at T1 compared to patients without a comorbid mood disorder ($t(73) = 2.47$, $d = 0.98$, $p = 0.016$).

3.3. Spectral quality

Exclusion of participants with low quality spectra did not affect demographical characteristics (see Table 1). There were no group differences in SNR and %CRLB for Glx and tNAA at any of the time points (see Table S3) and voxel placement was consistent over time and between groups (see Fig. 2A).

3.4. Glx concentrations

No differences in Glx concentrations were seen at the three time points between OCD patients and healthy controls (see Table 2). The LMM analyses between OCD patients and control participants did not show significant time ($F(2,66) = 1.08$, $\eta^2_p = 0.03$, $p = 0.35$), group ($F(1,46) = 0.98$, $\eta^2_p = 0.02$, $p = 0.33$) or time by group ($F(2,66) = 0.75$, $\eta^2_p = 0.02$, $p = 0.48$) effects. We also did not observe any main or interaction effects when comparing child and adult-onset OCD patients. Within OCD patients, there was no association between Y-BOCS score and Glx concentrations at any time point and no association between changes in Glx and changes in Y-BOCS over time (see Table S2).

3.5. tNAA concentrations

No differences in tNAA concentrations were seen between OCD patients and healthy controls at any of the time point (see Table 2). The LMM analyses between patients and healthy control did not reveal significant time ($F(2,76) = 0.34$, $\eta^2_p = 0.01$, $p = 0.72$), group ($F(1,47) = 0.68$, $\eta^2_p = 0.1$, $p = 0.43$) or time by group effects ($F(2,76) = 0.03$, $\eta^2_p < 0.01$, $p = 0.98$). Comparing childhood-onset with adult-onset OCD patients revealed a significant interaction between time and onset ($F(2,28) = 7.24$, $\eta^2_p = 0.27$, $p = 0.004$). Post-hoc tests showed that, compared to OCD patients with adult onset, patients with childhood onset had lower tNAA concentrations at both T0 ($t(49) = -2.94$, $d = -1{,}25$, $p = 0.005$) and T1 ($t(51) = -2.08$, $d = -0.93$, $p = 0.043$). Within the childhood onset group, a significant increase in tNAA was seen between T1 and T2 ($t(39) = 2.43$, $d = -0.86$, $p = 0.020$), and T0 and T2 ($t(39) = -2.31$, $d = -0.82$, $p = 0.026$). Conversely, tNAA concentration decreased between T0 and T2 in adult onset patients, ($t(42) = 2.78$, $d = 1.07$, $p = 0.008$) (see Fig. 3B and Table S5). Patients with childhood onset OCD were significantly younger compared to patients with adult OCD onset ($t(22) = 3.17$, $d = 1.35$, $p = 0.007$). However, the onset by time effect in OCD patients remained significant when adjusting for age ($F(2,40) = 7.28$, $\eta^2_p = 0.27$, $p = 0.004$). For demographic information on the childhood and adult onset group (see Table S7).

Y-BOCS score was not related to tNAA concentrations at any of the time points and tNAA changes did not correlate to changes in Y-BOCS score over time (see Table S2).

3.6. Exploratory analyses

Additionally, we looked into the effect of comorbid mood and anxiety disorders on neurometabolite levels. When comparing Glx

Table 2
Comparison of Glx and tNAA concentrations at baseline (T0), directly after treatment (T1) and three months post-treatment (T2) between OCD patients and healthy controls in the dACC. Glx and tNAA concentrations are expressed in Institutional Units (IU; mean ± SD), p-values are FDR corrected.

Time point	OCD patients	Healthy controls	*df*	*t*	*p*	*Cohen's d*
Glx						
T0	27.29 ± 2.62	28.41 ± 2.18	45	−1.58	0.36	−0.47
T1	28.26 ± 2.60	28.13 ± 2.38	35	0.16	0.88	0.05
T2	27.11 ± 2.20	27.87 ± 3.06	36	−0.88	0.58	−0.29
tNAA						
T0	18.06 ± 1.18	17.87 ± 1.02	45	0.61	0.76	0.18
T1	17.86 ± 0.82	17.76 ± 1.07	35	0.31	0.76	0.11
T2	17.96 ± 0.92	17.80 ± 1.37	36	0.43	0.76	0.14

Abbreviations: Glx, combination of glutamate and glutamine; tNAA, combination of N-acetylaspartate and N-acetyl-aspartyl-glutamate; T0, baseline; T1, directly after treatment; T2, three months after treatment.

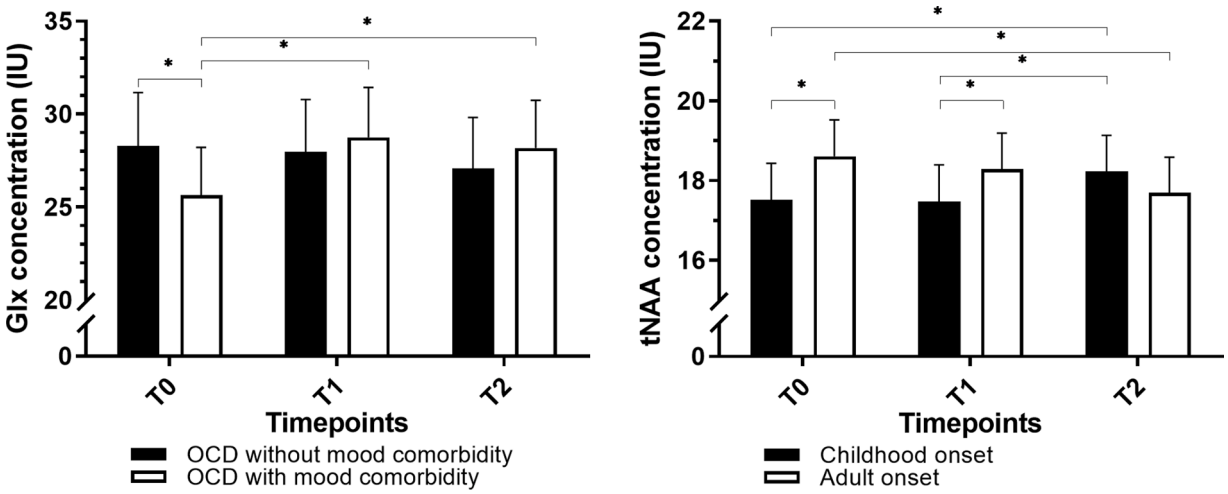

Fig. 3. Neurometabolite concentrations at baseline (T0), directly after treatment (T1) and three months after treatment (T2). (A) Glx concentration differences between OCD patients with mood comorbidity and patients without mood comorbidity over time. A significant increase in Glx was seen between T0-T1 in patients with mood comorbidity. At T0, patients with mood comorbidity had significantly lower Glx concentrations compared to patients without mood comorbidity. (B) tNAA concentration differences between patients with childhood and adult OCD onset. A significant increase in tNAA was seen between T1-T2 and T0-T2 in patients with childhood OCD onset. At T1 and T2, patients with childhood onset had significantly lower tNAA concentrations compared to patients with adult onset OCD. * $p < 0.05$.

concentrations in patients with and without mood comorbidity (while adjusting for medication status), no effects of time ($F(2,29) = 2.50$, $\eta^2_p = 0.30$, $p = 0.30$) or group were observed ($F(1,20) = 0.07$, $\eta^2_p < 0.01$, $p = 0.88$). We did, however, observe a significant group by time interaction ($F(2,29) = 5.16$, $\eta^2_p = 0.26$, $p = 0.036$), with post-hoc analyses showing that patients with a comorbid mood disorder had lower Glx concentrations at baseline compared to patients without a comorbid mood disorder ($t(38) = -2.28$, $d = -1.02$, $p = 0.028$). The lower concentrations at baseline in patients with a comorbid mood disorder increased between T0 and T1 ($t(33) = -3.09$, $d = -1.28$, $p = 0.004$) (see Fig. 3A, Table S5, and Table S6 for the demographics). For both Glx and tNAA, we did not observe any main or interaction effects between medicated versus non-medicated OCD patients or patients with and without a comorbid anxiety disorder (see Table S4).

LMM analyses did not reveal any differences in Glu, Gln, NAA, NAAG, Cr, Cho, and Ins concentration between OCD patients and healthy controls at baseline or over time. Also, no correlations were found between pre-treatment Glx and tNAA and PHQ-9, GAD-7, and OCI-R questionnaire scores at baseline.

4. Discussion

The current study investigated neurometabolite concentrations in the dACC in adult OCD patients compared to healthy controls at baseline, and changes directly after concentrated ERP and three months post-treatment. No Glx or tNAA differences between OCD patients and controls were found at baseline. In general, Glx and tNAA concentrations did not change over time and no correlations were found between Glx or tNAA concentrations and symptom improvement. When comparing patients with childhood onset and adult OCD onset of disease, childhood onset cases had lower tNAA concentrations at baseline, which increased three months after treatment. We also observed that OCD patients with a comorbid mood disorders had lower Glx concentrations at baseline and showed an increase in Glx directly after treatment. Conversely, Glx concentrations did not change following treatment in patients without a comorbid mood disorder.

Our results showed differences in tNAA concentrations between childhood and adult OCD onset groups. NAA is thought to be a marker for neuronal integrity and reductions of NAA might indicate neuronal loss (Moffett et al., 2014). The neurochemistry of adult patients with childhood onset OCD, and thus a very chronic course of disease, might exhibit more severe abnormalities in neuronal integrity, a hypothesis that fits with the finding that OCD patients show smaller ACC volumes (de Wit et al., 2014), and that longer illness duration is inversely correlated to total GM volume in OCD (Pujol et al., 2004). Interestingly, the increase and normalization of tNAA following treatment in the childhood onset group could indicate that the effect of chronicity on neuronal integrity is potentially reversible following treatment (Jang et al., 2006; Whiteside et al., 2012).

Previous studies did not find correlations between illness duration and (t)NAA concentrations in the ACC of OCD patients (Hatchondo et al., 2017; Jang et al., 2006). We relied on retrospective self-reports of onset which were dichotomized to adult (>18 years) or childhood (<18 years) onset as some patients were unable to report precisely when their OCD first developed. A recent study found that it takes a median of 7 years for subclinical symptoms to develop into a diagnosis of OCD (Thompson et al., 2020). This suggest that analyses on illness onset and duration should be interpreted with caution, as retrospective biases and gradual development might hinder a reliable estimation of onset.

Our findings are in line with previous studies that have demonstrated lower Glx concentrations in the ACC and anterior prefrontal regions in patients with major depressive disorder (MDD) (Hasler et al., 2007; Luykx et al., 2012; Rosenberg et al., 2005; Tadayonnejad et al., 2018), along with normalization after recovery (Hasler et al., 2005; Taylor et al., 2009). The possible effect of comorbid disorders on neurometabolite concentrations in OCD is further supported by studies reporting that NAA (Bedard and Chantal, 2011), Ins, and Cho concentrations (O'Neill et al., 2013, 2016) in the dACC are related to comorbid anxiety and depression in OCD patients. Other studies, however, did not report this association (Naaijen et al., 2017; Starck et al., 2008).

In general, the considerable variation in methods of MRS studies in OCD limits the comparison of the current findings with previous literature (Vester et al., 2020). Heterogeneity regarding medication status, comorbidity, and illness duration (Brennan et al., 2013), as well as the measurement and quality control of neurometabolites might result in different findings (Li et al., 2003). Nevertheless, the timing of the observed changes in Glx and tNAA concentrations after treatment are in line with our preregistered hypotheses. Changes in Glx after treatment in patients with mood comorbidity occurred swiftly (i.e. after one week), corresponding to the hypothesis that Glx concentrations regulate neuronal activity and might therefore change quickly over time (Govindaraju et al., 2000). The changes in tNAA were only observed

after three months post-treatment, possibly indicating slower processes such as changes in neuronal integrity and plasticity (Moffett et al., 2014).

4.1. Limitations

The current study has some limitations. The limited size of our OCD sample only enabled the detection moderate or large effect sizes (Button et al., 2013). The effect of medication status on metabolite concentrations remains unclear as we did not have extensive information on dosage and duration of medication use during and prior to the study (O'Neill et al., 2016; Yucel et al., 2007). However, even when this information was available for the current sample it remains difficult to reliably interpret medication effects given the limited size of the medicated subsample.

Besides this study's specific limitations, the field of 1H-MRS is subject to more general technical limitations, such as the difficulty to separate Glu and Gln at low field strengths due to overlapping resonance signals, resulting in the use of the pooled measure: Glx (Zhang and Shen, 2016). Although Glu and Gln are both involved in glutamatergic synthesis and neurotransmission, they fulfill different roles and interactions within this cycle. As a result, combining them into Glx causes loss of valuable information on Glu/Gln ratios which could potentially be informative (Yuksel and Ongur, 2010). Also, 1H-MRS at lower field strengths is limited to static measurements thereby losing information on underlying metabolite dynamics, whereas differences in metabolite concentrations between OCD patients and controls might be more strongly apparent during certain behavioural or pathological states. Both problems addressed above could potentially be solved with the use of ultra-high field 7T MR systems, possibly in combination with behavioural paradigms (Bednarik et al., 2015; Ip et al., 2017; Stanley and Raz, 2018).

5. Conclusions

To our knowledge, this is the first study investigating both direct (post-treatment) and delayed (follow-up) changes in neurometabolite concentrations after concentrated ERP in OCD patients. OCD patients with comorbid mood disorders showed lower Glx concentrations at baseline with an immediate increase after one week of concentrated ERP. Also onset of disease (childhood versus adult onset) was associated with differences tNAA changes over time. These heterogeneity effects, if replicated, should be take into account in future MRS studies, e.g. using (dynamic) metabolite measures at ultra-high field.

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CRediT authorship contribution statement

Niels T. de Joode: conceptualization and design of the work; analysis and interpretation of data; writing the original draft; editing of intellectual content. Anders L. Thorsen: conceptualization and design of the work; acquisition, analysis and interpretation of data; writing the original draft; editing of intellectual content. Eline L. Vester: conceptualization and design of the work; analysis and interpretation of data; writing the original draft; editing of intellectual content. Chris Vriend: conceptualization and design of the work; analysis and interpretation of data; writing the original draft; editing of intellectual content. Petra J.W. Pouwels: analysis and interpretation of data; editing of intellectual content. Kristen Hagen: acquisition and interpretation; editing of intellectual content. Olga T. Ousdal: acquisition and interpretation; editing of intellectual content. Bjarne Hansen: conceptualization and design of the work; analysis and interpretation of data; writing-original draft; editing of intellectual content; resources and funding acquisition. Gerd Kvale: conceptualization and design of the work; analysis and interpretation of data; writing-original draft; editing of intellectual content; resources and funding acquisition. Odile A. van den Heuvel: conceptualization and design of the work; analysis and interpretation of data; writing-original draft; editing of intellectual content; resources and funding acquisition.

None of the authors declare any competing interest with regards to this paper. All authors have read and approved its submission.

Supplementary materials

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References

Aoki, Y., Aoki, A., Suwa, H., 2012. Reduction of N-acetylaspartate in the medial prefrontal cortex correlated with symptom severity in obsessive-compulsive disorder: meta-analyses of (1)H-MRS studies. Transl. Psychiatry 2, e153.

Bedard, M.J., Chantal, S., 2011. Brain magnetic resonance spectroscopy in obsessive-compulsive disorder: the importance of considering subclinical symptoms of anxiety and depression. Psychiatry Res. 192, 45–54.

Bednarik, P., Tkac, I., Giove, F., DiNuzzo, M., Deelchand, D.K., Emir, U.E., Eberly, L.E., Mangia, S., 2015. Neurochemical and BOLD responses during neuronal activation measured in the human visual cortex at 7 Tesla. J. Cereb. Blood Flow Metab. 35, 601–610.

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. J. R. Stat. Soc. Series B-Stat. Methodol. 57, 289–300.

Bloch, M.H., Pittenger, C., 2010. The Genetics of Obsessive-Compulsive Disorder. Curr. Psychiatry Rev. 6, 91–103.

Brennan, B.P., Rauch, S.L., Jensen, J.E., Pope Jr., H.G., 2013. A critical review of magnetic resonance spectroscopy studies of obsessive-compulsive disorder. Biol. Psychiatry 73, 24–31.

Button, K.S., Ioannidis, J.P., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E.S., Munafo, M.R., 2013. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. 14, 365–376.

Cheng, Y., Xu, J., Nie, B., Luo, C., Yang, T., Li, H., Lu, J., Xu, L., Shan, B., Xu, X., 2013. Abnormal resting-state activities and functional connectivities of the anterior and the posterior cortexes in medication-naive patients with obsessive-compulsive disorder. PLoS ONE 8, e67478.

de Wit, S.J., Alonso, P., Schweren, L., Mataix-Cols, D., Lochner, C., Menchon, J.M., Stein, D.J., Fouche, J.P., Soriano-Mas, C., Sato, J.R., Hoexter, M.Q., Denys, D., Nakamae, T., Nishida, S., Kwon, J.S., Jang, J.H., Busatto, G.F., Cardoner, N., Cath, D. C., Fukui, K., Jung, W.H., Kim, S.N., Miguel, E.C., Narumoto, J., Phillips, M.L., Pujol, J., Remijnse, P.L., Sakai, Y., Shin, N.Y., Yamada, K., Veltman, D.J., van den Heuvel, O.A., 2014. Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. Am. J. Psychiatry 171, 340–349.

Fan, S., Cath, D.C., van den Heuvel, O.A., van der Werf, Y.D., Schols, C., Veltman, D.J., Pouwels, P.J.W., 2017. Abnormalities in metabolite concentrations in tourette's disorder and obsessive-compulsive disorder-A proton magnetic resonance spectroscopy study. Psychoneuroendocrinology 77, 211–217.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview For DSM-IV-TR Axis I Disorders, Research version, Patient Edition (SCID I/P). Biometrics Research, New York State Psychiatric Institute, New York, NY.

Fitzgerald, K.D., Welsh, R.C., Gehring, W.J., Abelson, J.L., Himle, J.A., Liberzon, I., Taylor, S.F., 2005. Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. Biol. Psychiatry 57, 287–294.

Foa, E.B., Huppert, J.D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., Salkovskis, P.M., 2002. The Obsessive-Compulsive Inventory: development and validation of a short version. Psychol. Assess. 14, 485–496.

Gallop, R., Tasca, G.A., 2009. Multilevel modeling of longitudinal data for psychotherapy researchers: II. the complexities. Psychother. Res. 19, 438–452.

Gnanavel, S., Sharan, P., Khandelwal, S., Sharma, U., Jagannathan, N.R., 2014. Neurochemicals measured by (1)H-MR spectroscopy: putative vulnerability biomarkers for obsessive compulsive disorder. MAGMA 27, 407–417.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox, P.T., Etkin, A., 2015. Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry 72, 305–315.
Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch. Gen. Psychiatry 46, 1006–1011.
Govindaraju, V., Young, K., Maudsley, A.A., 2000. Proton NMR chemical shifts and coupling constants for brain metabolites. NMR Biomed. 13, 129–153.
Hansen, B., Hagen, K., Ost, L.G., Solem, S., Kvale, G., 2018. The Bergen 4-Day OCD Treatment Delivered in a Group Setting: 12-Month Follow-Up. Front. Psychol. 9, 639.
Hansen, B., Kvale, G., Hagen, K., Havnen, A., Ost, L.G., 2019. The Bergen 4-day treatment for OCD: four years follow-up of concentrated ERP in a clinical mental health setting. Cogn. Behav. Ther. 48, 89–105.
Hasler, G., Neumeister, A., van der Veen, J.W., Tumonis, T., Bain, E.E., Shen, J., Drevets, W.C., Charney, D.S., 2005. Normal prefrontal gamma-aminobutyric acid levels in remitted depressed subjects determined by proton magnetic resonance spectroscopy. Biol. Psychiatry 58, 969–973.
Hasler, G., van der Veen, J., Tumonis, T., Meyers, N., Shen, J., Drevets, W.C., 2007. Reduced Prefrontal Glutamate/Glutamine and γ-Aminobutyric Acid Levels in Major Depression Determined Using Proton Magnetic Resonance Spectroscopy. Arch. Gen. Psychiatry 64, 193–200.
Hatchondo, L., Jaafari, N., Langbour, N., Maillochaud, S., Herpe, G., Guillevin, R., Guillevin, C., 2017. (1)H magnetic resonance spectroscopy suggests neural membrane alteration in specific regions involved in obsessive-compulsive disorder. Psychiatry Res. Neuroimaging 269, 48–53.
Havnen, A., Hansen, B., Ost, L.G., Kvale, G., 2014. Concentrated ERP delivered in a group setting: an effectiveness study. J. Obsess.-Compuls. Rel. 3, 319–324.
Havnen, A., Hansen, B., Ost, L.G., Kvale, G., 2017. Concentrated ERP Delivered in a Group Setting: a Replication Study. Behav. Cogn. Psychother. 45, 530–536.
Ip, I.B., Berrington, A., Hess, A.T., Parker, A.J., Emir, U.E., Bridge, H., 2017. Combined fMRI-MRS acquires simultaneous glutamate and BOLD-fMRI signals in the human brain. Neuroimage 155, 113–119.
Jakubovski, E., Diniz, J.B., Valerio, C., Fossaluza, V., Belotto-Silva, C., Gorenstein, C., Miguel, E., Shavitt, R.G., 2013. Clinical predictors of long-term outcome in obsessive-compulsive disorder. Depress. Anxiety 30, 763–772.
Jang, J.H., Kwon, J.S., Jang, D.P., Moon, W.J., Lee, J.M., Ha, T.H., Chung, E.C., Kim, I.Y., Kim, S.I., 2006. A proton MRSI study of brain N-acetylaspartate level after 12 weeks of citalopram treatment in drug-naive patients with obsessive-compulsive disorder. Am. J. Psychiatry 163, 1202–1207.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17, 825–841.
Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., 2012. Fsl. Neuroimage 62, 782–790.
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5, 143–156.
Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16, 606–613.
Launes, G., Hagen, K., Sunde, T., Ost, L.G., Klovning, I., Laukvik, I.L., Himle, J.A., Solem, S., Hystad, S.W., Hansen, B., Kvale, G., 2019. A Randomized Controlled Trial of Concentrated ERP, Self-Help and Waiting List for Obsessive- Compulsive Disorder: the Bergen 4-Day Treatment. Front. Psychol. 10, 2500.
Li, B.S.Y., Wang, H., Gonen, O., 2003. Metabolite ratios to assumed stable creatine level may confound the quantification of proton brain MR spectroscopy. Magn. Reson. Imaging 21, 923–928.
Littell, R.C., Pendergast, J., Natarajan, R., 2000. Modelling covariance structure in the analysis of repeated measures data. Stat. Med. 19, 1793–1819.
Luykx, J.J., Laban, K.G., van den Heuvel, M.P., Boks, M.P., Mandl, R.C., Kahn, R.S., Bakker, S.C., 2012. Region and state specific glutamate downregulation in major depressive disorder: a meta-analysis of (1)H-MRS findings. Neurosci. Biobehav. Rev. 36, 198–205.
Maltby, N., Tolin, D.F., Worhunsky, P., O'Keefe, T.M., Kiehl, K.A., 2005. Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. Neuroimage 24, 495–503.
Marsh, R., Horga, G., Parashar, N., Wang, Z., Peterson, B.S., Simpson, H.B., 2014. Altered activation in fronto-striatal circuits during sequential processing of conflict in unmedicated adults with obsessive-compulsive disorder. Biol. Psychiatry 75, 615–622.
Mataix-Cols, D., Fernandez de la Cruz, L., Nordsletten, A.E., Lenhard, F., Isomura, K., Simpson, H.B., 2016. Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. World Psychiatry 15, 80–81.
McGovern, R.A., Sheth, S.A., 2017. Role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder: converging evidence from cognitive neuroscience and psychiatric neurosurgery. J. Neurosurg. 126, 132–147.
Moffett, J.R., Ariyannur, P., Arun, P., Namboodiri, A.M.A., 2014. N-Acetylaspartate and N-Acetylaspartylglutamate in Central Nervous System Health and Disease, Magnetic Resonance Spectroscopy. Academic Press, San Diego, pp. 71-90.
Naaijen, J., Zwiers, M.P., Amiri, H., Williams, S.C.R., Durston, S., Oranje, B., Brandeis, D., Boecker-Schlier, R., Ruf, M., Wolf, I., Banaschewski, T., Glennon, J.C., Franke, B., Buitelaar, J.K., Lythgoe, D.J., 2017. Fronto-striatal glutamate in autism spectrum disorder and obsessive compulsive disorder. Neuropsychopharmacology 42, 2456–2465.
O'Neill, J., Gorbis, E., Feusner, J.D., Yip, J.C., Chang, S., Maidment, K.M., Levitt, J.G., Salamon, N., Ringman, J.M., Saxena, S., 2013. Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive-compulsive disorder. J. Psychiatr. Res. 47, 494–504.
O'Neill, J., Lai, T.M., Sheen, C., Salgari, G.C., Ly, R., Armstrong, C., Chang, S., Levitt, J. G., Salamon, N., Alger, J.R., Feusner, J.D., 2016. Cingulate and thalamic metabolites in obsessive-compulsive disorder. Psychiatry Res. Neuroimaging 254, 34–40.
O'Neill, J., Piacentini, J., Chang, S., Ly, R., Lai, T.M., Armstrong, C.C., Bergman, L., Rozenman, M., Peris, T., Vreeland, A., Mudgway, R., Levitt, J.G., Salamon, N., Posse, S., Hellemann, G.S., Alger, J.R., McCracken, J.T., Nurmi, E.L., 2017. Glutamate in Pediatric Obsessive-Compulsive Disorder and Response to Cognitive-Behavioral Therapy: randomized Clinical Trial. Neuropsychopharmacology 42, 2414–2422.
Ortiz, A.E., Ortiz, A.G., Falcon, C., Morer, A., Plana, M.T., Bargallo, N., Lazaro, L., 2015. 1H-MRS of the anterior cingulate cortex in childhood and adolescent obsessive-compulsive disorder: a case-control study. Eur. Neuropsychopharmacol. 25, 60–68.
Ost, L.G., Havnen, A., Hansen, B., Kvale, G., 2015. Cognitive behavioral treatments of obsessive-compulsive disorder. A systematic review and meta-analysis of studies published 1993-2014. Clin. Psychol. Rev. 40, 156–169.
Pauls, D.L., Abramovitch, A., Rauch, S.L., Geller, D.A., 2014. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat. Rev. Neurosci. 15, 410–424.
Petroff, O.A., 2002. GABA and glutamate in the human brain. Neuroscientist 8, 562–573.
Pico-Perez, M., Moreira, P.S., de Melo Ferreira, V., Radua, J., Mataix-Cols, D., Sousa, N., Soriano-Mas, C., Morgado, P., 2020. Modality-specific overlaps in brain structure and function in obsessive-compulsive disorder: multimodal meta-analysis of case-control MRI studies. Neurosci. Biobehav. Rev. 112, 83–94.
Pittenger, C., 2015. Glutamatergic agents for OCD and related disorders. Curr. Treat. Options Psychiatry 2, 271–283.
Pittenger, C., Bloch, M.H., Williams, K., 2011. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. Pharmacol. Ther. 132, 314–332.
Provencher, S.W., 1993. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn. Reson. Med. 30, 672–679.
Provencher, S.W., 2001. Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR Biomed. 14, 260–264.
Pujol, J., Soriano-Mas, C., Alonso, P., Cardoner, N., Menchon, J.M., Deus, J., Vallejo, J., 2004. Mapping structural brain alterations in obsessive-compulsive disorder. Arch. Gen. Psychiatry 61, 720–730.
Radua, J., van den Heuvel, O.A., Surguladze, S., Mataix-Cols, D., 2010. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch. Gen. Psychiatry 67, 701–711.
Rosenberg, D.R., Macmaster, F.P., Mirza, Y., Smith, J.M., Easter, P.C., Banerjee, S.P., Bhandari, R., Boyd, C., Lynch, M., Rose, M., Ivey, J., Villafuerte, R.A., Moore, G.J., Renshaw, P., 2005. Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study. Biol. Psychiatry 58, 700–704.
Rosenberg, D.R., Mirza, Y., Russell, A., Tang, J., Smith, J.M., Banerjee, S.P., Bhandari, R., Rose, M., Ivey, J., Boyd, C., Moore, G.J., 2004. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. J. Am. Acad. Child Adolesc. Psychiatry 43, 1146–1153.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155.
Spitzer, R.L., Kroenke, K., Williams, J.B., Lowe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166, 1092–1097.
Stanley, J.A., Raz, N., 2018. Functional Magnetic Resonance Spectroscopy: the "New" MRS for Cognitive Neuroscience and Psychiatry Research. Front. Psychiatry 9, 76.
Starck, G., Ljungberg, M., Nilsson, M., Jonsson, L., Lundberg, S., Ivarsson, T., Ribbelin, S., Ekholm, S., Carlsson, A., Forssell-Aronsson, E., Carlsson, M.L., 2008. A 1H magnetic resonance spectroscopy study in adults with obsessive compulsive disorder: relationship between metabolite concentrations and symptom severity. J. Neural Transm. (Vienna) 115, 1051–1062.
Stein, D.J., Costa, D.L.C., Lochner, C., Miguel, E.C., Reddy, Y.C.J., Shavitt, R.G., van den Heuvel, O.A., Simpson, H.B., 2019. Obsessive-compulsive disorder. Nat. Rev. Dis. Primers 5, 52.
Tadayonnejad, R., Deshpande, R., Ajilore, O., Moody, T., Morfini, F., Ly, R., O'Neill, J., Feusner, J.D., 2018. Pregenual Anterior Cingulate Dysfunction Associated with Depression in OCD: an Integrated Multimodal fMRI/(1)H MRS Study. Neuropsychopharmacology 43, 1146–1155.
Tasca, G.A., Gallop, R., 2009. Multilevel modeling of longitudinal data for psychotherapy researchers: I. the basics. Psychother. Res. 19, 429–437.
Taylor, M.J., Selvaraj, S., Norbury, R., Jezzard, P., Cowen, P.J., 2009. Normal glutamate but elevated myo-inositol in anterior cingulate cortex in recovered depressed patients. J. Affect. Disord. 119, 186–189.
Thompson, E.M., Torres, A.R., Albertella, L., Ferrao, Y.A., Tiego, J., Shavitt, R.G., Conceicao do Rosario, M., Miguel, E.C., Fontenelle, L.F., 2020. The speed of progression towards obsessive-compulsive disorder. J. Affect. Disord. 264, 181–186.
Thorsen, A.L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., van den Heuvel, O.A., 2018. Emotional processing in obsessive-compulsive disorder: a systematic review and meta-analysis of 25 functional neuroimaging studies. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 3, 563–571.
Tukel, R., Aydin, K., Ertekin, E., Ozyildirim, S.S., Taravari, V., 2014. Proton magnetic resonance spectroscopy in obsessive-compulsive disorder: evidence for reduced neuronal integrity in the anterior cingulate. Psychiatry Res. 224, 275–280.
van den Heuvel, O.A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S.R., Nakamae, T., Denys, D., Goudriaan, A.E., Veltman, D.J., 2016. Brain circuitry of compulsivity. Eur. Neuropsychopharmacol. 26, 810–827.

van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Cath, D.C., van Balkom, A.J., van Hartskamp, J., Barkhof, F., van Dyck, R., 2005. Frontal-striatal dysfunction during planning in obsessive-compulsive disorder. Arch. Gen. Psychiatry 62, 301–309.

Vester, E.L., de Joode, N.T., Vriend, C., Pouwels, P.J.W., van den Heuvel, O.A., 2020. Little evidence for neurometabolite alterations in obsessive-compulsive disorder - a systematic review of magnetic resonance spectroscopy studies at 3 Tesla. J. Obsess.-Compuls. Rel. 25.

Wang, R., Fan, Q., Zhang, Z., Chen, Y., Tong, S., Li, Y., 2017. White matter integrity correlates with choline level in dorsal anterior cingulate cortex of obsessive compulsive disorder patients: a combined DTI-MRS study. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. 3521–3524, 2017.

Whiteside, S.P., Abramowitz, J.S., Port, J.D., 2012. The effect of behavior therapy on caudate N-acetyl-L-aspartic acid in adults with obsessive-compulsive disorder. Psychiatry Res. 201, 10–16.

Yucel, M., Harrison, B.J., Wood, S.J., Fornito, A., Wellard, R.M., Pujol, J., Clarke, K., Phillips, M.L., Kyrios, M., Velakoulis, D., Pantelis, C., 2007. Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. Arch. Gen. Psychiatry 64, 946–955.

Yucel, M., Wood, S.J., Wellard, R.M., Harrison, B.J., Fornito, A., Pujol, J., Velakoulis, D., Pantelis, C., 2008. Anterior cingulate glutamate-glutamine levels predict symptom severity in women with obsessive-compulsive disorder. Aust. N. Z. J. Psychiatry 42, 467–477.

Yuksel, C., Ongur, D., 2010. Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. Biol. Psychiatry 68, 785–794.

Zhang, Y., Brady, M., Smith, S., 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Trans. Med. Imaging 20, 45–57.

Zhang, Y., Shen, J., 2016. Simultaneous quantification of glutamate and glutamine by J-modulated spectroscopy at 3 Tesla. Magn. Reson. Med. 76, 725–732.

Zhang, Z., Fan, Q., Bai, Y., Wang, Z., Zhang, H., Xiao, Z., 2016. Brain Gamma-Aminobutyric Acid (GABA) Concentration of the Prefrontal Lobe in Unmedicated Patients with Obsessive-Compulsive Disorder: a Research of Magnetic Resonance Spectroscopy. Shanghai Arch. Psychiatry 28, 263–270.

Zurowski, B., Kordon, A., Weber-Fahr, W., Voderholzer, U., Kuelz, A.K., Freyer, T., Wahl, K., Buchel, C., Hohagen, F., 2012. Relevance of orbitofrontal neurochemistry for the outcome of cognitive-behavioural therapy in patients with obsessive-compulsive disorder. Eur. Arch. Psychiatry Clin. Neurosci. 262, 617–624.