Eur Arch Psychiatry Clin Neurosci (2012) 262:617–624
DOI 10.1007/s00406-012-0304-0

ORIGINAL PAPER

Relevance of orbitofrontal neurochemistry for the outcome of cognitive-behavioural therapy in patients with obsessive–compulsive disorder

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Received: 16 August 2011 / Accepted: 24 February 2012 / Published online: 17 March 2012

Abstract Since the advent of non-invasive methods such as proton magnetic resonance spectroscopy (^{1}H-MRS), obsessive–compulsive disorder (OCD) has been increasingly associated with an altered composition of neurometabolites and neurotransmitters in several brain areas. Particularly, Inositol has not only been implicated in OCD pathophysiology, but also shown effective in pilot studies in therapy-refractory OCD patients. However, the relevance of regional brain neurochemistry for therapy outcome has not yet been investigated. Whereas numerous neuroimaging findings support a dysfunction of the orbitofrontal cortex (OFC) in OCD, MR-spectroscopic investigations of this region are missing. ^{1}H-MRS and psychometric measurements were obtained from twenty unmedicated patients with OCD, subsequently enrolled in a 3-month structured inpatient cognitive-behavioural therapy programme, and from eleven matched control subjects. Multiple regression of symptom score changes (Y-BOCS) on (*myo*-)inositol concentrations in three areas (right orbitofrontal cortex (OFC), right striatum and anterior cingulate cortex) was performed. The concentration of (*myo*-)inositol in the OFC only predicted the outcome of subsequent CBT regarding Y-BOCS score reduction (Spearman's $r_s = .81$, $P < 0.003$, corrected). The (*myo*-)inositol concentration did not differ between OCD patients and healthy controls and did not change during therapy. We provide preliminary evidence for a neurochemical marker that may prove informative about a patient's future benefit from behaviour therapy. Inositol, a metabolite involved in cellular signal transduction and a spectroscopic marker of glial activity, predicted the response to CBT selectively in the OFC, adding to the evidence for OFC involvement in OCD and highlighting neurobiological underpinnings of psychotherapy.

Keywords OCD · CBT · Magnetic resonance spectroscopy · Orbitofrontal cortex · Inositol · Glia

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Electronic supplementary material The online version of this article (doi:10.1007/s00406-012-0304-0) contains supplementary material, which is available to authorized users.

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Introduction

Orbitofrontal neurochemistry, and particularly the (*myo*-)inositol concentration, has been reported to be closely correlated with anxiety scores in healthy subjects [15]. First, inositol's derivatives are components of the phosphoinositide (PI) pathway, which is an important second messenger system in the brain, modulating neuronal excitability and synaptic plasticity [10]. Second, inositol is

important for the cells' osmoregulation. Finally, due to its predominance in astroglia, (*myo*-)inositol serves as an MR-spectroscopic marker indicating pathologically increased glial activity and proliferation in several neuropsychiatric diseases [10, 17, 19]. Despite the predominant role of the orbitofrontal cortex (OFC) in the pathophysiology of OCD, its neurochemistry has not been investigated using ^{1}H-MRS to date, particularly in the context of therapy. In OCD, the (lateral) orbitofrontal cortex has repeatedly been shown to be overactive in resting state studies of blood flow and metabolism and showed reduced task-related activation in studies probing the OFC with fMRI [7, 11, 23, 31]. Importantly, Saxena et al. [32] and Busatto et al. [5] reported reductions of right orbitofrontal metabolism after paroxetine and behavioural therapy, respectively. Moreover, reduction of orbitofrontal metabolism was correlated with symptom reduction. Lower OFC metabolism predicted greater response to pharmacological treatment in four studies [4, 30, 32, 35]. Finally, structural (orbito)frontal abnormalities changes have been observed using manual and voxel-based morphometry and, recently, using gyrification indices as a measure of implied developmental disturbances [38]. Motivated by these observations, we used ^{1}H-MRS to investigate the concentration of (*myo*-)inositol in the lateral OFC in relation to the course of cognitive-behavioural therapy (CBT). We target the lateral (Brodmann's area (BA) 47) rather than the medial (BA 11) OFC, which is supported by earlier findings in OCD, in part, and particularly motivated by a meta-analysis of 87 functional imaging studies probing the OFC in healthy subjects [20]. This meta-analysis has revealed a functional medio-lateral dissociation with evaluation of positive outcomes of actions found in the medial OFC (BA 11) and evaluation of negative outcomes of actions found in the lateral OFC (BA 47). The latter process presenting with elevated harm-avoidant thinking and behaviour is prominent in patients with OCD [12].

In the present study, we target a neurometabolite which shares a number of features particularly relevant in the context of CBT in OCD: (*Myo*)-inositol (1) is reliably measurable with MRS [33], (2) serves as an MR-spectroscopic marker of glial activity [10, 19], (3) is pathophysiologically conceptualized in OCD research [17], and (4) has shown therapeutic effects in OCD [6, 13]. The first criterion is particularly important in the context of repeated measurements in the course of therapy. The second criterion makes (*myo*-)inositol interesting in the context of neuroplasticity as a neuronal correlate of CBT with exposure and response prevention, given the relevance of glial function for neuroplasticity [1, 26]. The third criterion renders (*myo*-)inositol unique among detectable compounds using ^{1}H-MRS, since inositol has shown effects as medication in open and controlled trials in therapy-refractory OCD [6, 13]. Since (*myo*-)inositol is increased in several neuropsychiatric diseases, possibly indicating pathologically increased glial activity [10, 19], we tested the hypothesis that patients with OCD show higher orbitofrontal (*myo*-)inositol concentrations than controls. Secondly, we hypothesized that elevated (*myo*-)inositol levels normalize over the course of therapy. Previous neuroimaging studies suggest that higher orbitofrontal metabolism predicts poorer therapy outcome. We thus expected patients with higher orbitofrontal (*myo*-)inositol levels—presumably indicating higher levels of dysfunction [34]—to show poorer symptom reduction, according to change of total Y-BOCS score.

Method

Subjects and treatment

Patients were recruited through our outpatient service and enrolled in a CBT programme at our inpatient unit specialized in OCD. Patients remained in hospital during the whole study period. In accordance with the Helsinki convention, all subjects gave informed consent to participate. The study was approved by the Ethics Committee of the University of Lübeck. Twenty unmedicated OCD patients were scanned and clinically evaluated at admission and after 3 months of structured CBT in a specialized inpatient unit. Evaluation included diagnosis confirmation, criteria for inclusion and exclusion, assessment of co-morbid disorders and symptom severity. Diagnosis of OCD was confirmed using Structured Clinical Interview for DSM-IV (SCID). SCID was applied by therapists experienced in the therapy of OCD only. All of them have completed certified SCID training. Inclusion criteria were as follows: age 18–65, pre-treatment Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) [14] total score $\geq$16, right-handedness according to the Edinburgh Handedness Inventory [25]. Exclusion criteria were as follows: current moderate or severe episode of major depression, history of schizophrenia spectrum disorders, history of drug abuse or dependence (Structured Clinical Interview for DSM-IV), present psychoactive medication (washout $\geq$4 weeks), major medical conditions, history of major head injury or neurological disorders. One patient met criteria for ADHD and two met criteria for a mild depressive episode. None of the patients received antidepressants or other psychoactive medication during the study. 13 out of 16 patients were naïve regarding psychoactive medication. Following accepted standards, obsessive compulsive symptoms were assessed using the Y-BOCS, and subjects with 35% or more reduction and 'much improved' or 'very much improved' on Clinical Global Impression/Improvement Scale (CGI) were identified as responders. This widely

used but arbitrary criterion was applied only to allow comparison with other studies, it did not guide statistical analyses or results. For the assessment of depressive symptoms (secondary outcome variable), the Hamilton Depression Rating Scale (HDRS) [16] was used. Healthy right-handed control subjects with no history of psychiatric or neurological disorder, dementia, concurrent major medical disorder or major head injury and the usual MRI contraindications were recruited through personal contact and advertisement. Only control subjects were paid for the participation. In contrast to patients, ^{1}H-MRS was performed only once in healthy controls ($n = 11$). During the recruitment period, no hardware changes to the scanner were applied and stability of relevant parameters was checked by MR-physicist on a weekly basis. Only eleven control subjects were scanned because of a major scanner upgrade. We stopped recruitment subsequently because data acquired after the upgrade would likely include a systematic error.

Patients had 50-min individual CBT sessions twice weekly (24 total) according to a structured manual. All therapists were experienced in CBT for OCD and completed a pre-study training in order to maximize manual adherence. Individual CBT sessions included education and cognitive restructuring techniques, with main emphasis on exposure and response prevention.

Acquisition of MR spectra

^{1}H-MRS was performed using a PRESS sequence (TE = 30 ms, TR = 3,000 ms, NEX = 128) on a 3 Tesla magnet (Siemens Trio, Erlangen, Germany) equipped with an 8-channel coil (PAT). In addition to an auto shim routine, manual shimming was performed for each 2-cm^3 voxel. Voxels were placed (1) in the right lateral OFC (Supplemental Fig. S1), (2) in rostral anterior cingulate cortex (ACC) including both hemispheres and (3) in the right ventral striatum. Without hypothesizing a hemispheric lateralization of pathology in OCD, we scanned only the right side due to time limitations. For the purpose of absolute quantification, three spectra were acquired for each voxel: a water suppressed in vivo spectrum, a non-suppressed fully relaxed water signal (TR = 10 s, NEX = 4) and, finally, the non-suppressed, fully relaxed water signal from the same voxel using the body coil in transmit-receive mode. A high-resolution (1 × 1 × 1 mm) T1-weighted whole brain volume preceded acquisition of ^{1}H-spectra.

Data post-processing

Post-processing of spectra was done offline using Matlab® 6.5 software (MathWorks, Natick, MA). Spectra from each of the 8 coil channels were stored uncombined. For a pseudo-absolute quantification of the spectra using a receive only coil, a method similar to that described previously by Natt et al. [24] was used: The non-suppressed water spectra from each coil element were used for the estimation of phase differences φ_k and weighting factors w_k of each coil element as well as for eddy-current correction. Metabolite spectra were summated according to

$$S_{\text{sum}} = \sum_{k=1}^{8} w_k \cdot S_k e^{-i\varphi_k}$$

The amplitude of the spectra was then normalized to the transmitter reference voltage of the body coil TA_{BC} using the amplitude of the summated water signal received by the 8-channel receiver coil A_{sum}^{H20} and the water signal received by the body coil A_{BC}^{H20} by

$$TA_{\text{sum}} = \frac{A_{\text{sum}}^{H20}}{A_{BC}^{H20}} TA_{BC}.$$

The processed and normalized in vivo data were analysed using linear combinations of model in vitro spectra (LCModel; Version 6.1-0) [28]. To provide prior information for the analysis of in vivo spectra, a phantom database from MRS acquisitions of aqueous solutions of 27 compounds was created. Finally, metabolite concentrations were corrected for the brain tissue content of the given voxel, shifted to the position corresponding to the chemical shift displacement for each metabolite frequency, respectively. The values for the tissue types were derived by segmenting the high-resolution anatomical data. We have described the applied segmentation and correction algorithms in detail elsewhere [36]. Following common standards, only estimated metabolite concentrations with Cramer-Rao lower bands <20% (standard deviation, SD) in the LCModel fit (Fig. 1) were included in the group analysis [28]. Consequently, four patients and two control subjects were excluded from the final analysis due to poor quality of spectra. This left a sample of 16 patients and nine control subjects (see Table 1).

Because data quality may have influenced the respective metabolite levels (for example, due to potential symptom-related movement of the subject's head), we tested for a correlation of (*myo*-)inositol levels and their respective SD of the fit.

Statistical testing was performed using Statistica® (StatSoft, Tulsa, USA). Multiple regression of Y-BOCS (difference) scores on (*myo*-)inositol concentrations was applied (1) for the OFC and (2) for all data with 'region' ($n = 3$; OFC, ACC, striatum) as factor. Student's *t* tests were applied to test for effects of 'group' (patients vs. controls; unpaired) and effects of 'time' (before vs. after therapy; paired) within OFC as target region. Additionally, analysis of variance (ANOVA) with 'group' and 'region' as factors was applied to test for overall differences (1) at baseline, between patients and controls and (2) within patients, between the two time points.

Results

Therapy outcome

OC symptoms, as assessed using the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS), decreased by 12.9 (mean, SD ± 3.6) points or 49.5%, from a score of 26.1 (±3.7) at admission to 13.2 (±3.1) after 3 months of intensive CBT (paired $t(15) = 14.4$, $P < 10^{-6}$). 14 out of 16 patients were identified as CBT responders according to the pre-defined criteria. In both non-responders, the Y-BOCS score decreased by 20 and 25%, respectively. There were no significant differences between the original ($n = 20$) and the final ($n = 16$) patient sample regarding demographic or psychopathological characteristics (Y-BOCS 26.1 (±3.7) vs. 26.0 (±3.4); Y-BOCS reduction 12.94 (±3.59) vs. 12.9 (±3.34).

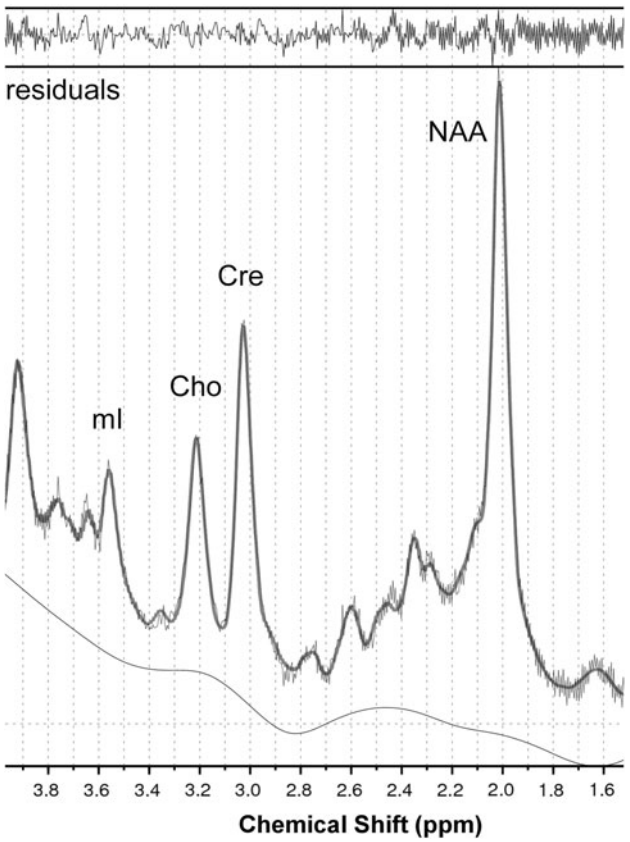

Fig. 1 Representative sample orbitofrontal (OFC) ^{1}H-MRS spectrum from an OCD patient. The *fine grey line* shows the original Fourier-transformed data. The superimposed *thick grey line* shows the spectral fit by Linear Combination of Metabolites Basis Spectra (LCModel). Residuals from the spectral fit are shown on top of the figure. The *fine grey line* below the spectrum depicts the 'baseline'. *ppm* parts per million, *MI* (*myo*-)inositol, *Cho* choline, *Cr* Creatine, *NAA* N-acetyl aspartate

Spectroscopy

As expected, ACC spectra showed better quality than spectra from striatum and OFC. For the patient group ($n = 16$), mean standard deviation of the fit for (*myo*-)inositol was 7.6% (±2.9) for OFC, 8.1% (±2.8) for striatum and 4.9% (±0.9) for ACC, indicating very good data quality overall (Fig. 1). Levels of metabolites were not significantly correlated with their SD of the fit (all Ps > 0.2), indicating that individual metabolite levels were not confounded by data quality. Most importantly, inclusion of the four subjects excluded due to poor quality of spectra did not remove any of the significances reported and no new significances appeared (all Ps > 0.2).

Correlation with outcome

The orbitofrontal (*myo*-)inositol level was highly negatively correlated with symptom improvement according to Y-BOCS change after CBT (Spearman's $r_s = -0.81$, $P < 0.003$, corrected for the number of areas ($n = 3$) and metabolites ($n = 5$) acquired; $P < 0.0002$, uncorrected; Fig. 2). This association was highly specific to the OFC (multiple regression; Ps > 0.3 for other regions). Baseline orbitofrontal (*myo*-)inositol levels explained 69.2% (corrected) of the variance in subsequent symptom change ([Y-BOCSpre − Y-BOCSpost]). Multiple regression analysis including all ($n = 5$) acquired metabolites revealed that (*myo*-)inositol is a better predictor of symptom change than other metabolites. Inclusion of all metabolites moderately

Table 1 Demographic and clinical characteristics

	Patients ($N = 16$)	Controls ($N = 9$)	Differences
Age (years)	34.0 (±10.8)	32.67 (±12.04)	$t = 0.28$; $P > 0.7$.
Sex (female:male)	12:4	7:2	$\chi^2 = 0.02$; $P > 0.8$
Education (years)	13.44 (±2.19)	15.0 (±2.19)	$t = 1.7$; $P > 0.1$
Duration of OCD (years)	9.57 (±10.5)	n.a.	n.a.
Y-BOCS-score	26.0 (±3.4)	n.a.	n.a.
HAMD-score	5.2 (±4.02)	n.a.	n.a.
Y-BOCS-score post	13.1 (±3.1)	n.a.	n.a.
CBT Response Rate[a]	87.5% (14/16)	n.a.	n.a.

[a] Response criterion: At least 35% symptom reduction according to Y-BOCS

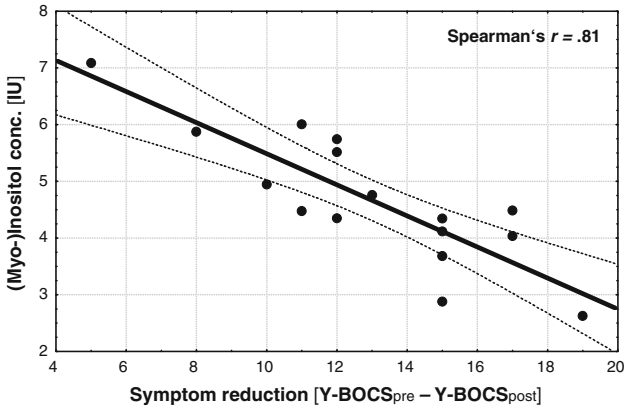

Fig. 2 Negative correlation between (*myo*-)inositol concentration in the right orbitofrontal cortex and improvement of obsessive–compulsive symptoms as defined by the difference between individual scores on the Yale-Brown Obsessive–Compulsive Scale before and after therapy ($\text{Y-BOCS}_{\text{pre}} - \text{Y-BOCS}_{\text{post}}$) in $n = 16$ patients. *Thick line* linear least square fit. *Dotted lines* 95% confidence intervals. *IU* independent units

increased explained variance to 83.8% (69.2% for (*myo*-)inositol alone). However, in contrast to (*myo*-)inositol ($P < 0.003$), individual Spearman's correlations of all other metabolites ($n = 3$) showing significant beta-values in the multiple regression model did not reach significance: creatine ($P > 0.07$), choline ($P > 0.1$) and glutamate ($P > 0.9$; all *P*s corrected). Notably, (*myo*-)inositol was clearly a better predictor of symptom change than baseline Y-BOCS score (n.s.; $P > 0.1$). This is important, because greater reductions might have been simply the consequence of higher initial Y-BOCS scores being more likely to fall *per se*, on the one hand. On the other hand, however, very high initial Y-BOCS scores might have been associated with therapy resistance. The (*myo*-)inositol concentration in the OFC was not correlated with age ($r_s = -0.03$; $P > 0.9$) or with the duration of illness ($r_s = 0.05$; $P > 0.8$). Finally, the (*myo*-)inositol concentration did not correlate with changes in symptoms of depression (Spearman's $r_s = 0.14$; $P > 0.6$; Hamilton Depression Rating Scale, HDRS).

Group comparison

Analysis of variance (2-factorial ANOVA) revealed an effect of 'group' on (*myo*-)inositol levels ($F(1,67) = 4.56$; $P < 0.04$) across regions (OFC, ACC, striatum). This moderate effect did not remain significant when Bonferroni correction for the number of testable metabolites was applied, however ($P > 0.1$). Non-significantly higher (*myo*-)inositol levels were observed in patients (mean 4.86 IU) than in controls (mean 4.33 IU) across voxels, without a significant interaction between the factors 'group' and 'region' ($F(1,67) = 0.11$; $P > 0.8$). In each one of the three regions at study, (*myo*-)inositol levels were nominally higher in patients than in controls, without reaching statistical significance. Particularly, orbitofrontal (*myo*-)inositol levels did not significantly differ between patients at baseline (mean 4.9 IU) and a matched healthy control group (mean 4.27 IU; $t(19) = 1.17$; $P > 0.8$).

Pre–post comparison

MR spectra from 12 (16) patients were ultimately included in the pre–post comparison. Two subjects completed treatment but refused a second scan. Data from two other subjects were excluded due to insufficient quality (see 'Method' for criterion). ANOVA for repeated measures did not reveal a significant effect of 'time' on (*myo*-)inositol levels across regions (OFC, ACC, striatum; $F(1,43) = 1.3$; $P > 0.3$). Particularly, we did not find a significant difference between (*myo*-)inositol concentrations in the OFC before CBT (mean 4.9 IU; SD 1.17) and after CBT (mean 4.81 IU; SD 0.87; paired $t(11) = 0.23$; $P > 0.8$).

Discussion

Using proton MR spectroscopy with absolute quantification, we identified a strong neurobiological predictor of response to CBT in a sample of sixteen unmedicated patients with OCD without co-morbid depression. The (*myo*-)inositol concentration in the orbitofrontal cortex only predicted response to CBT. This effect was specific for symptom reduction according to Y-BOCS and was not observed for reduction of depressive symptoms according to HDRS. The orbitofrontal (*myo*-)inositol concentration did not differ between OCD patients and healthy controls and did not change after successful therapy in the patient group.

To what extent is our observation physiologically plausible? We will first discuss the tested hypotheses in the light of previous findings from ^{1}H-MRS studies in OCD. We will then place our results in the context of neuroimaging findings supporting a predominant role of the (lateral) OFC in both the pathophysiology and therapy of OCD. We will then discuss the specific role of (*myo*-)inositol for neural signalling and neuroplasticity, as a neural correlate of behaviour therapy. Finally, we will suggest how these—at times disparate—lines of evidence may converge.

(*Myo*-)inositol in OCD

Despite the lack of existing MRS data from the OFC and longitudinal measurements of (*myo*-)inositol in OCD, our results are in line with previous MRS investigations generally showing no significant differences in (*myo*-)

inositol levels between patients and controls in other regions [34, 39], [27] for review. Our results thus argue against a role of (*myo*-)inositol as a *marker* of disease, extending previous negative findings to the OFC. Although (*myo*-)inositol levels were consistently higher in all three regions in patients than in controls, this difference did not reach significance for any of the regions. One might speculate, however, that the observed mean difference of 12.7% for the OFC indicates a moderate but meaningful effect to be confirmed in larger samples.

Regarding our second hypothesis, there were no changes in (*myo*-)inositol concentrations over the course of therapy among patients, arguing against a role of (*myo*-)inositol as a neural *correlate* of symptom change. The two studies investigating changes of metabolite levels in the course of any therapy in OCD suggest that such changes are both metabolite-specific [18] and region-specific [2]. Jang et al. [18] obtained measurements from six cortical regions and observed an increase in initially reduced N-Acetyl-Aspartate(NAA)/Creatine ratio in frontal regions including ACC after 12 weeks of therapy with citalopram. This effect was not found in the posterior cingulate cortex or in the parietal cortex, however. It also did not seem to apply to Choline/Creatine ratio. Absolute quantification was not performed in this study, and (*myo*-)inositol was not included. In contrast, in the most comparable study to ours, Benazon et al. [2] did investigate (*myo*-)inositol in the caudate nucleus, but also did not find significant changes in the course of CBT in 15 children with OCD. Nevertheless, (*myo*-)inositol concentration dropped by nearly 9.9% after CBT. One might therefore speculate that the non-significant reductions observed in the Benazon et al. study ($n = 15$) and in our present study ($n = 12$; 4.9 vs. 4.81 IU) might become significant in larger samples. Such observation would be in line with our highly significant finding of *lower* (*myo*-)inositol levels predicting *better* outcome from CBT.

The present results suggest that the role of (*myo*-)inositol in OCD is confined to a *predictor* of OC symptom change in the context of CBT, or therapy in general. Although a notable predictive value was observed for other metabolites for the OFC, significance was reached for (*myo*-)inositol only. This observation was, moreover, anatomically confined to the OFC voxel. In other words, any single metabolite in the ACC or in the striatum was significantly correlated with OC symptom change. Interestingly, Starck et al. [34] reported a positive correlation between Y-BOCS score and (*myo*-)inositol levels—but not other metabolites—in the occipital cortex of OCD patients. The relevance of (*myo*-)inositol is also supported by the report of a strong correlation between (*myo*-)inositol levels and anxiety in healthy subjects [15], with (*myo*-)inositol being not uniquely but most strongly correlated with symptom severity.

The orbitofrontal cortex in OCD

Our results concur with measurements of regional cerebral glucose utilization in OCD patients, repeatedly highlighting the importance of the OFC [23], particularly in the context of psychotherapy [22]. Previous studies using PET have demonstrated reductions of increased orbitofrontal metabolism following both pharmacotherapy and CBT [4, 5, 32, 35]. Most importantly, our observation concurs with replicated findings of a predictive value of orbitofrontal glucose metabolism for later response to pharmacological treatment of OCD [4, 30, 32, 35]. Patients with higher baseline metabolism showed poorer response to SSRIs in these three studies. In contrast, Brody et al. found higher baseline orbitofrontal metabolism to predict better response in a CBT-treated group, but worse response in a fluoxetine-treated group.

Perhaps the most convincing findings from congnitive neuroscience of OCD come from fMRI applications of the reversal learning paradigm probing adaptive rule switching upon negative and positive feedback [7, 31]. Remijnse et al. were able to link lateral orbitofrontal dysfunction during this task to the time periods where OCD patients received negative feedback. Recently, we were able to replicate the finding of a reversal learning deficit in OCD and OFC dysfunction as its major cortical substrate [11]. In all three studies, patients showed a poor task-related recruitment of the lateral portion of the OFC (mainly Brodmann's area 47), bilaterally. Moreover, Chamberlain et al. have suggested a genetic source of orbitofrontal reversal learning deficits, showing their presence in unaffected siblings of OCD patients to a lesser degree. Most relevant in the context of the present study, however, is the partial reversibility of orbitofrontal dysfunction over the course of CBT, as observed by Freyer et al. using fMRI [11]. Menzies et al. confirmed a dysfunction of the lateral orbitofrontal cortex in OCD upon a statistical meta-analysis of functional MRI studies across cognitive paradigms [23]. This is not surprising, given that all cognitive paradigms employed involved some form of repeated evaluation and prediction of positive versus negative outcomes of actions and given that patients with OCD are often preoccupied with preventing harm and negative outcomes of actions to occur [12]. Such cognitive processes are supported by the lateral OFC and are critically impaired in patients with OFC lesions [20].

(*Myo*-)inositol signalling, neuroplasticity and behavioural change

Due to its predominance in astroglia, (*myo*-)inositol serves as an MR-spectroscopic marker indicating glial activity and proliferation in several neuropsychiatric diseases

[10, 17, 19]. Undoubtedly, normal glial function is crucial for learning and neuroplasticity, since learning-dependent synaptic strengths are controlled by astrocytes [1, 26]. Glial influences on synaptic transmission are presumably relevant for the success of behavioural therapy, given that effects of CBT may be boosted with the supplementation of the gliotransmitter D-serine in OCD [37] and anxiety disorders. In the present context, (*myo*-)inositol might indicate the integrity of glial mechanisms subserving cellular and synaptic plasticity [1, 10, 26], as involved in fear extinction and operant (de-)conditioning during CBT [21, 22].

Inositol has been shown to be effective in a small placebo-controlled and cross-over designed trial in OCD [13] and two open trials [6], whereas it was ineffective as add-on medication. It appears counterintuitive that patients with *lower* pre-treatment (*myo*-)inositol levels show *larger* benefits from CBT. However, behavioural and biochemical studies indicate that efficacy of inositol does not simply involve the replenishing of the membrane phosphoinositide (PI) pool [17, 29]. Given that the mechanism of action is still under debate, our finding of *higher* (*myo*-)inositol in poor responders does not contradict therapy studies conducted on inositol to date.

(*Myo*-)inositol alters receptor sensitivity and can direct membrane trafficking events [17]. Serotonergic neuromodulation may provide a meaningful link between (*myo*-)inositol signalling and orbitofrontal dysfunction in OCD. 5-HT2C-Receptor hypersensitivity has been found in patients with OCD [8] and is supported by animal models of OCD [3]. Exogenous (*myo*-)inositol has been shown to reduce 5-HT2-Receptor desensitization in animal studies [29] Interestingly, in contrast to other areas, infusion of a 5-HT2C antagonist into the orbitofrontal cortex only improved performance in an animal model of reversal learning [3], a task crucially dependent on OFC function and typically impaired in OCD patients [7, 31]. We recently reported that orbitofrontal dysfunction associated with this task may be reversible after CBT [11].

Dysregulation of the phosphoinositide pathway as related to deficient serotonergic function [17] and hypermetabolism of the lateral orbitofrontal cortex [23] have both been independently postulated as major components of OCD pathophysiology. Moreover, based on the findings in healthy relatives of OCD patients, both have been proposed as vulnerability markers or endophenotypes of OCD [7, 9]. As suggested above, an important effector of (*myo*-)inositol signalling, 5-HT2 receptor function within the OFC crucially regulates cognitive performance in reversal learning and, presumably, other relevant cognitive operations depending on the OFC [3, 20]. These most likely include evaluation and prediction of positive and negative outcomes of actions during repeated exposure and response management over the course of CBT.

Limitations

The small sample size and the lack of a waiting list arm constitute important limitations of the study. In particular, correlates of CBT effects and correlates of symptom remission cannot be disentangled. Regarding the observed prediction specificity for the lateral OFC, one should bear in mind that only three regions were scanned, excluding other regions more or less relevant for OCD: thalamus, insula, amygdala or dorsal PFC. Finally, we should mention that meaningful functional changes of (*myo*-)inositol are not necessarily detectable with ^{1}H-MRS, given that this method is insensitive to changes in intracellular versus extracellular concentrations or in (*myo*-)inositol distribution between intracellular compartments.

Conclusion

Overall, we have identified a promising, anatomically confined candidate biological predictor of CBT response in a sample of unmedicated, non-depressed patients with OCD—the (*myo*-)inositol concentration in the lateral orbitofrontal cortex. Extended investigations into the relationship between orbitofrontal function, inositol and different therapeutic regimens in OCD constitute necessary and worthwhile endeavours.

Acknowledgments This research was supported by the Deutsche Forschungsgemeinschaft (DFG, Grants BR 1766/4-2 and VO 542/1-2). We thank Jane Klemen and Eszter Schoell for helpful comments.

Conflict of interest The authors declare that they have no conflict of interest.

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