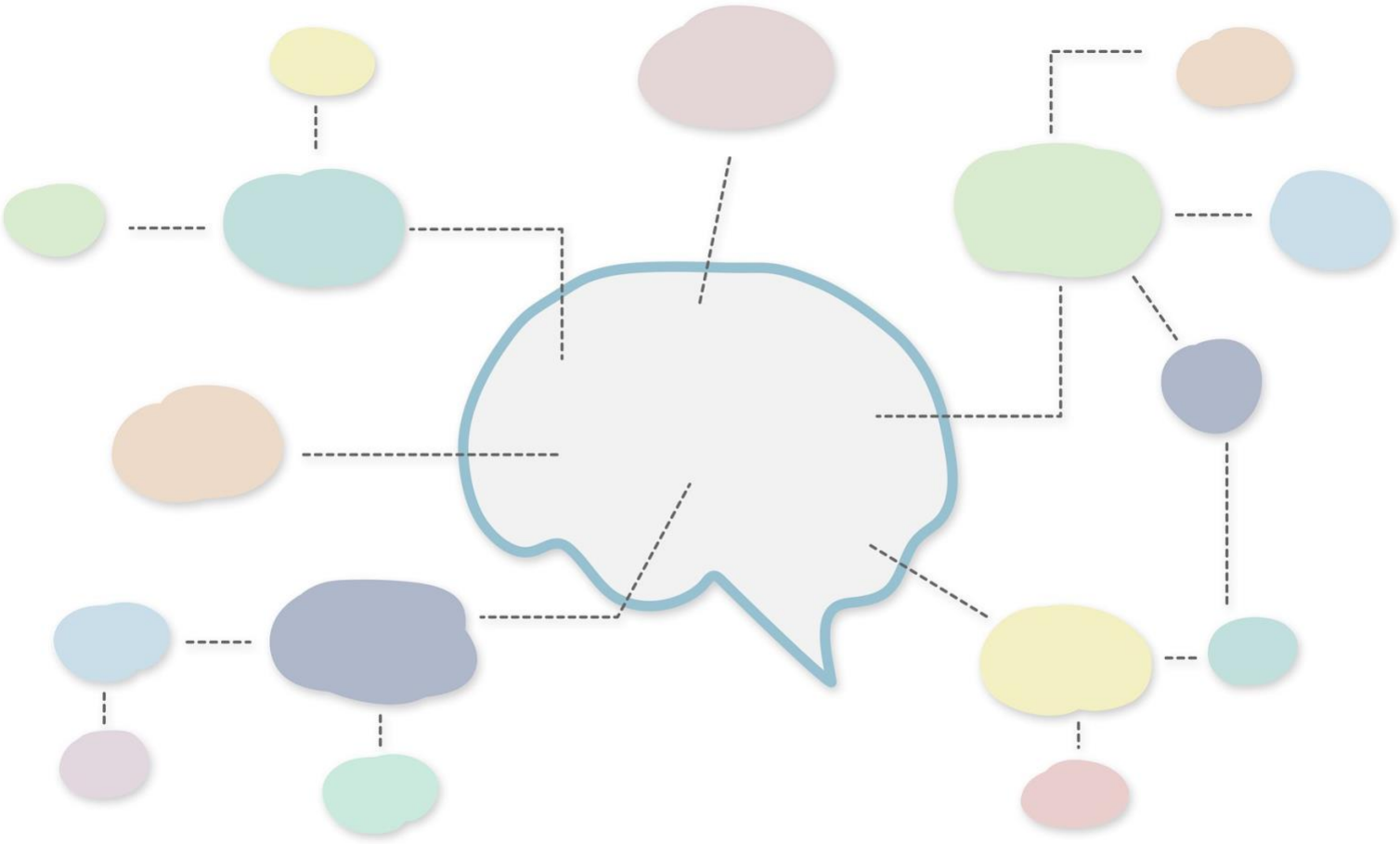
Mindful
Continuing Education

Therapeutic Interventions for Obsessive-Compulsive Disorder



Brain serotonin synthesis capacity in obsessive-compulsive disorder: effects of cognitive behavioral therapy and sertraline

Abstract

Cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are both effective treatments for some patients with obsessive-compulsive disorder (OCD), yet little is known about the neurochemical changes related to these treatment modalities. Here, we used positron emission tomography and the α-[^{11}C]methyl-L-tryptophan tracer to examine the changes in brain regional serotonin synthesis capacity in OCD patients following treatment with CBT or SSRI treatment. Sixteen medication-free OCD patients were randomly assigned to 12 weeks of either CBT or sertraline treatment. Pre-to-post treatment changes in the α-[^{11}C]methyl-L-tryptophan brain trapping constant, K^* (ml/g/min), were assessed as a function of symptom response, and correlations with symptom improvement were examined. Responders/partial responders to treatment did not show significant changes in relative regional tracer uptake; rather, in responders/partial responders, 12 weeks of treatment led to serotonin synthesis capacity increases that were brain-wide. Irrespective of treatment modality, baseline serotonin synthesis capacity in the raphe nuclei correlated positively with clinical improvement. These observations suggest that, for some patients, successful remediation of OCD symptoms might be associated with greater serotonergic tone.

Introduction

Obsessive-compulsive disorder (OCD) is a chronic mental illness involving intrusive, unwanted thoughts (obsessions) and persistent mental or behavioral rituals (compulsions) that cause significant deficits in social functioning. Cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) have, in separate multicenter trials, demonstrated efficacy and tolerability in the treatment of 40–60% of OCD patients[1,2]. The success of SSRIs, relative to medications targeting neurotransmitter systems other than serotonin (5-hydroxytryptamine (5-HT)), suggests that the latter may play a role in the remediation of OCD symptoms[3,4]. Despite the documented effectiveness of these treatments, changes in neurochemistry in vivo associated with CBT or SSRI in OCD patients, including changes in the serotonergic system, remain *elusive*.

Neuroimaging and neurosurgical studies have implicated the cortico-striato-thalamo-cortical (CSTC) circuit in OCD neurobiology[5]; indeed, effective OCD treatments with either SSRIs, clomipramine, or behavior therapy, alone or in combination, have been reported to decrease abnormally elevated CSTC circuit activity[6,7]. Notably, however, conflicting findings have been reported, including increased activity within CSTC circuitry following successful OCD treatment[8]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have investigated more specific aspects of neurotransmission within CSTC circuitry, including measuring 5-HT transporter (5-HTT)

and receptor binding, using tracers such as [^{11}C]DASB, [^{123}I]β-CIT, [^{11}C]McN 5652, and [^{11}C]MDL100907. Pre-treatment, baseline abnormalities in 5-HTT and 5-HT$_{2A}$ receptor availabilities within CSTC circuitry have been reported in OCD patients[9–11], although there has been considerable variability[12–14].

To date, few studies have investigated changes in the serotonergic system during OCD treatment. Early studies found changes in cerebrospinal fluid 5-HT metabolite levels and blood platelet 5-HTT levels pre–post treatment[15], but these findings have not been replicated[16], and peripheral 5-HT measures cannot be used to study brain regional changes in serotonergic functioning. To our knowledge, only one study has investigated within-subject brain regional changes in the serotonergic system in OCD patients before and after treatment: Zitterl et al. reported a significant reduction in 5-HTT availability in the thalamus/hypothalamus of OCD patients, using SPECT and [^{123}I]β-CIT, following 12 weeks of clomipramine treatment[17]. Similar decreases during repeated exposure to SSRIs in various pathological and non-pathological conditions were also reviewed[17]. To our knowledge, no studies have explored the effects of CBT on the serotonergic system in OCD patients. Moreover, 5-HTT imaging has been interpreted by many to reflect density of innervation, rather than functional status per se[18].

The PET tracer α-[^{11}C]methyl-L-tryptophan (α-[^{11}C]MTrp) is thought to reflect central 5-HT metabolism in humans in vivo[19,20]. α-[^{11}C]MTrp is analogous to the 5-HT precursor, L-tryptophan, except that it is not incorporated into protein[21]. After crossing the blood-brain barrier, α-[^{11}C]MTrp is taken up into serotonergic neurons, and ultimately is metabolized into α-M-5-HT. α-M-5-HT is not degraded by monoamine oxidase and cannot cross the blood–brain barrier, thereby accumulating in serotonergic neurons. The net blood-to-brain clearance of the tracer is used to calculate the α-[^{11}C]MTrp trapping (unidirectional uptake) constant, K^* (in ml/g/min). α-[^{11}C]MTrp has been used to study 5-HT synthesis capa-city, and more generally, 5-HT metabolism, in various patient populations[22–24]. In particular, we previously used α-[^{11}C]MTrp to study baseline 5-HT synthesis capacity rates in OCD patients, and reported abnormally elevated α-[^{11}C]MTrp trapping, relative to controls, in temporal, striatal, and limbic regions[25].

As a follow-up to our baseline study of treatment-free OCD patients, the present study investigated the effects of drug treatment or CBT on brain regional 5-HT synthesis capacity. OCD patients were randomly assigned to either CBT or SSRI monotherapy (sertraline), and α-[^{11}C]MTrp PET scans were repeated following 12 weeks of treatment. The goals of the present study were to (i) compare regional 5-HT synthesis capacity in OCD patients before and after treatment with CBT or sertraline, and (ii) identify brain regions where pre-treatment regional 5-HT synthesis capacity is associated with treatment outcome. Here, we expected that changes in α-[^{11}C]MTrp uptake, particularly within CSTC circuitry, would relate to changes in obsessive-compulsive, but not mood, symptoms. However, as the first study of treatment-related changes in serotonin synthesis capacity in OCD patients, the current study was designed to be primarily exploratory in nature.

Materials and methods

Study population

Patients were referred by the OCD Clinic, Department of Psychology, McGill University Health Center (MUHC), having participated in a baseline PET study prior to beginning treatment[25]. Exclusion criteria included: (1) personal or family history of Tourette's syndrome; (2) history of other Axis I disorders, except for depression secondary to OCD, as assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[26]; (3) current or past substance abuse or dependence; (4) current or past use of 3,4-methylene-dioxy-methamphetamine (MDMA) or methylene-dioxy-amphetamine (MDA); and (5) history of allergy or treatment resistance to sertraline. All patients, at entry into the study, were medication-free for at least 3 weeks or more than five elimination half-lives of the drug, whichever was longer. Most patients were medication-free for considerably longer; of eight patients previously treated with antidepressants, seven were drug-free >6 months at entry into the study.

After inclusion in the study, the patients were randomly assigned (using a block randomization design with blocks of 4) to receive CBT or sertraline treatment for a period of 12 weeks. OCD symptom severity, assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and depressive symptoms, estimated with the Beck Depression Inventory (BDI), were recorded by a clinician blind to the patient's PET data approximately every 2 weeks during treatment, beginning at baseline (week 0). Following completion of the 12-week treatment study, patients in both groups were offered further treatment as clinically indicated.

All participants provided written, informed consent. The study was carried out in accordance with the Declaration of Helsinki, and was approved by the Research Ethics Committee of the Montreal Neurological Institute (MNI) and the Institutional Review Board of McGill University.

Treatment

Patients assigned to sertraline treatment received an initial dose of 25 mg/day. Sertraline was provided in an open fashion, as 25 mg capsules ingested once daily, in the

morning with food. After 1 week of treatment, unless limited by side effects, the daily dose was increased to 50 mg/day. If, after a second week, the patient's ther-apeutic response did not show evidence of symptomatic improvement, this dose was increased to 100 mg/day unless limited by side effects. A third increase in dose to 150 mg/day after another 2 weeks (week 4) and a final increase to 200 mg/day (week 6) were each made if response remained unsatisfactory (<20% decrease in Y-BOCS score). The final mean ± SD daily dose of sertraline was 133 ± 52 mg/day, and all patients were prescribed a stable dose of medication during the last 2 weeks of the study.

Patients assigned to CBT received two 90-min individual sessions per week for 12 weeks. Specialized CBT was designed and administered under the close supervision of DS, an experienced OCD expert clinician and supervisor. The specialty multidimensional CBT program was individualized for each patient and included: psycho-education; cognitive therapy to collaboratively modify symptom-related appraisals and meanings of intrusive thoughts and feared situations; strategies for dysfunc-tional cognitive–emotional processing, intolerance of distress, and overestimation of threat; exposure and response prevention (ERP) and behavioral experiment protocols designed to optimize adaptive learning; self-directed, between-session homework with attention to treatment adherence; and interventions for relapse pre-vention, resilience, and self-efficacy. Therapist-assisted ERP and behavioral experiments were administered in patients' home as needed. Interventions specifically tar-geted the symptom subtype characteristics for each case[27].

PET and magnetic resonance imaging (MRI)

PET scans were performed before and after 12 weeks of treatment. PET and MRI procedures were carried out as per Berney et al.[25]. Briefly, in order to minimize variability between scans in plasma concentrations of amino acids, such as tryptophan, a low-protein diet followed by an overnight fast was required of participants before scanning days[28]. On PET scan days, all participants tested negative on a urine drug screen sensitive to cocaine, opiates, phencyclidine, cannabinoids, barbiturates, benzodiazepines, and amphetamines (Triage Panel for Drugs of Abuse, Biosite Diagnostics, CA, USA). Additionally, women of fertile age were scanned during their follicular phase, due to previous findings of changes in serotonergic activity in different phases of the estrous cycle in rats[29] and the menstrual cycle in women[30].

α-[^{11}C]MTrp was produced as described elsewhere[31]. PET scanning was performed using an ECAT HR+ scanner (CTI/Siemens, Knoxville, TN; 3D mode with a resolution of 5 × 5 × 5 mm full width at half maximum (FWHM)) in the late morning/early afternoon. After a transmission scan for attenuation correction using a ^{68}Ge/Ga source, α-[11C]MTrp was injected intravenously over 2 min (mean ± SD = 9.6 ± 0.8 mCi), and a 60-min dynamic image acquisition scan was performed. Thirteen venous blood samples were collected to compute the α-[^{11}C]MTrp input function, as described previously[32,33]. Five plasma samples were used to measure free and total plasma tryptophan concentrations using high-performance liquid chromatography.

Each participant also underwent a T_1-weighted MRI scan for PET-MR co-registration using a 1.5 T Philips Gyroscan scanner (Philips Medical Systems, Eindhoven, Netherlands; 3D fast-field echo scan: TR = 18 ms; TE = 10 ms; FA = 30°; 256 × 256 × 160 mm matrix; 1 mm^3 isotropic resolution).

Calculation of α-[^{11}C]MTrp trapping (*K**)

The Patlak graphic approach[34] was used to calculate absolute K^* values (ml/g/min), using dynamic PET data collected 20–60 min after tracer injection[32,33] and peripheral metabolite values. To account for any effect of global differences in α-[^{11}C]MTrp trapping on regional values, relative regional K^* values were calculated by normalizing absolute regional K^* values to global K^* values (defined as the mean K^* value for gray matter). Given that both relative and absolute K^* values were previously reported to be stable over several weeks within an individual[35], we also examined within-subject changes in absolute regional K^* values. Pre- and post-treatment comparisons of regional and global K^* values were carried out using both Statistical Parametric Mapping (SPM) and an MRI-based region of interest (ROI) method.

Voxel-based analysis using SPM

Brain-wide voxel-wise analyses comparing K^* values pre- and post-treatment were carried out using SPM12 (Wellcome Functional Imaging Laboratory). K^* images were spatially normalized into MNI-305 stereotaxic space, using an algorithm described elsewhere[36], and then smoothed using a 14-mm FWHM Gaussian filter to reduce the effect of anatomical variability. The t-test was applied voxel by voxel. The height threshold used to interpret the t-test in terms of probability level was set at $p < 0.001$, uncorrected for multiple comparisons, with an extent threshold of 100 voxels, as previously[25], then at 50 voxels for exploratory analyses. The t-map threshold was $T_8 = 4.50$ for responders/partial responders and $T_5 = 5.89$ for non-responders.

MRI-based ROI analysis

Pre–post treatment changes in regional K^* values were also analyzed using an a priori MRI-based ROI approach. Each patient's MRI data were corrected for field inhomogeneities and spatially normalized into MNI-305

stereotaxic space. Using an automatic segmentation method[37,38], ROIs were defined in the left and right caudate, hippocampus, inferior temporal gyrus, cingulate, lateral and medial prefrontal cortices, nucleus accumbens, putamen, and thalamus. ROIs were smoothed using a 7 mm FWHM Gaussian filter and resampled into PET acquisition space. Time–activity curves were then derived by applying the ROIs to dynamic native PET space.

Results

Demographics

Sixteen patients with a diagnosis of OCD as per the SCID[26] were included in the study. After randomization, eight patients received CBT (6M/2F), and eight sertraline (6M/2F). Data from a post-treatment PET scan were not available for one male patient treated with CBT for technical reasons, therefore a total of 15 patients was included in all PET analyses (11M/4F; mean ± SD age = 34.4 ± 9.3 years).

The demographic and clinical characteristics of the OCD patients are summarized in Table 1 for each treat-ment subgroup, and in Supplementary Table 1 for each clinical response subgroup. No significant differences in age, Y-BOCS score, or BDI score were found prior to treatment between treatment subgroups, or between subgroups of "responders & partial responders" vs. "non-responders".

Clinical response

We observed a progressive improvement in mean Y-BOCS scores for both treatment groups, as illustrated in Fig. 1. At 12 weeks of continuous monitoring of clinical response, seven patients were deemed responders to treatment (≥35% decrease in Y-BOCS score), and three patients were deemed partial responders to treatment (≥25% but ≤35% reduction in Y-BOCS score)[39]; these 10 patients were combined into a group of responders/partial responders to treatment for all analyses (4 CBT/6 SSRI; mean ± SD % decrease in Y-BOCS score = 52.5 ± 20.1). Six patients were deemed non-responders to treatment (4 CBT/2 SSRI; <25% decrease in Y-BOCS score; mean ± SD % decrease = 1.9 ± 22.4). Overall, there was a significant decrease in Y-BOCS scores pre–post treatment (two-tailed paired *t*-test; $t_{15} = 4.49$, $p < 0.001$); there was no significant difference between CBT and SSRI treatment groups in the pre–post % change in Y-BOCS scores (two-tailed independent *t*-test, $t_{14} = 0.72$, $p = 0.48$). In the whole sample, BDI scores pre–post treatment *decreased* significantly (Wilcoxon signed-rank test, $Z = -2.2$, $p = 0.026$), though the effect was clinically minimal.

Global and regional α-[^{11}C]MTrp trapping

Using SPM analysis, the functional images of all OCD patients from pre- and post-treatment conditions were first compared (Pre > Post and Pre < Post). No significant changes in relative (normalized) or absolute regional K^* values were observed when treatment groups were combined. Accordingly, no ROIs demonstrated a significant pre–post change in relative or absolute K^* values in the ROI-based analyses, and further, there was no significant pre–post change in global K^* values in the whole patient sample. Similarly, when pre- and post-treatment α-[^{11}C]MTrp trapping was compared within each treatment group separately (sertraline or CBT), no relative or absolute regional or global changes in K^* values were identified.

Next, we compared pre- and post-treatment α-[^{11}C]MTrp trapping in the sub-sample of responders/partial responders ($n = 9$) and non-responders ($n = 6$). Using SPM and ROI-based analyses, again, no significant pre–post changes in relative regional K^* values were identified in treatment responders. However, responders/

Table 1 Patient demographics

Characteristic	CBT ($n = 8$)		SSRI ($n = 8$)	
Age, y				
Mean (SD)	33.7 (9.5)		33.4 (8.5)	
Range	23–53		18–45	
Responders/partial responders	4/8		6/8	
Early-onset OCD (≤10 y), No.	5		5	
Predominant compulsion, No.				
Washing	4		4	
Checking	4		4	
Lifetime history of MDE (2° to OCD symptoms), No.	2		3	
Past substance abuse, No.	0		0	
	Pre	Post	Pre	Post
Y-BOCS score, mean (SD)	23 (4.4)	15.8 (7.5)	23.6 (5.6)	14.7 (8.2)
BDI score, mean (SD)	9.8 (4.5)	6.9 (6.0)	14.1 (11.2)	7.6 (9.5)
Plasma free tryptophan, mean (SD), nmol/L[a]	10.3 (2.6)	8.4 (1.4)	9.8 (1.7)	9.3 (2.1)
Global K^*, mean (SD), mL/g/min[a]	5.1 (1.3)	6.1 (1.5)	5.8 (1.3)	6.07 (2.0)
Intravenously injected, mean (SD), mCi[a]	9.3 (1.1)	9.6 (0.7)	9.6 (0.8)	9.7 (0.4)

Responders/partial responders demonstrated a >25% decrease in Y-BOCS score
OCD obsessive-compulsive disorder, *CBT* cognitive behavioral therapy, *SSRI* selective serotonin re-uptake inhibitor, *MDE* major depressive episode, *Y-BOCS* Yale-Brown Obsessive Compulsive Scale, *BDI* Beck Depression Inventory, *No.* number
[a]Data not included for one patient treated with CBT

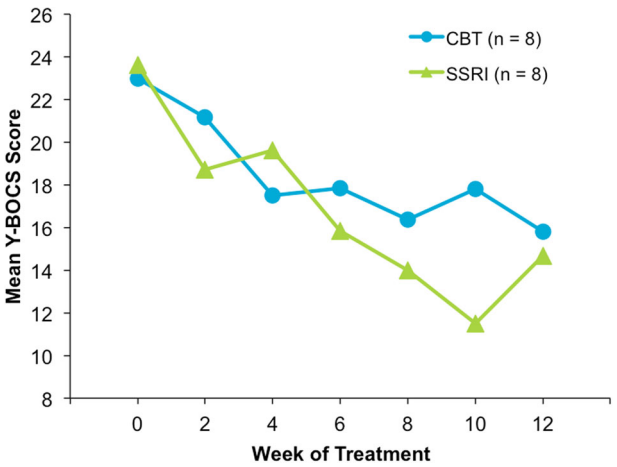


Fig. 1 OCD symptom improvement over time with CBT or sertraline treatment. Change in mean Y-BOCS scores during 12 weeks of CBT or sertraline treatment, as measured approximately every 2 weeks. Y-BOCS Yale-Brown Obsessive Compulsive Scale, CBT cognitive behavioral therapy, SSRI selective serotonin re-uptake inhibitor

partial responders demonstrated a significant increase in global K^* values pre–post treatment (two-tailed paired t-test, $t_8 = 3.05$, $p = 0.016$; mean increase of 29.7%, Cohen's $d = 1.02$), whereas non-responders showed no significant treatment-related changes in global K^* values (two-tailed paired t-test, $t_5 = 0.63$, $p = 0.55$; mean decrease of 6.4%). Pre-treatment values of global K^* did not differ significantly between responders/partial responders and non-responders. Correspondingly, voxel-wise analyses identified brain-wide increases in absolute K^* values (right » left; yet, increases in absolute K^* values were observed bilaterally in the ROI analyses, see Supplementary Figure 1) in responders/partial responders pre–post treatment (Fig. 2a). By contrast, no changes in absolute K^* values were observed in non-responders, pre–post treatment (Fig. 2b).

A three-way Time × ROI × Response repeated measures ANOVA yielded a significant Time × Response interaction ($F_{1,13} = 5.67$, $p = 0.033$) but not a three-way interaction ($p = 0.61$), indicating that the effects did not differ in the separate ROIs. Consistent with this, the change in global K^* values pre–post treatment was significantly greater in the responders/partial responders than the non-responders (two-tailed independent t-test, $t_{13} = 2.37$, $p = 0.034$, Hedges' $g = 1.25$).

Correlations between α-[^{11}C]MTrp trapping and clinical scores

Using SPM analysis and ΔY-BOCS scores as a covariate, we evaluated the correlation between ΔY-BOCS scores and pre-treatment K^* values in the whole patient sample. Both baseline K^* and ΔY-BOCS values were normally distributed. Improvement in Y-BOCS scores correlated positively with baseline α-[^{11}C]MTrp trapping in the raphe nuclei within the right midbrain ($t_{13} = 6.66$, $k = 67$ voxels, coordinates x, y, $z = 6$, -20, -22 mm) independent of treatment modality (Fig. 3).

Consistent with the global K^* value findings in clinical response sub-groups, pre–post treatment changes in global K^* values (ΔK^*_{Global}) correlated positively with % decrease in Y-BOCS scores ($r_s = 0.46$, $p = 0.08$), as shown in Fig. 4. Notably, there was a clear outlier in this correlation, and when the outlier was removed, the correlation reached significance ($r_s = 0.67$, $p = 0.009$). ΔBDI scores did not correlate with pre–post treatment changes in global K^* values ($r_s = -0.01$, $p = 0.96$) or with ΔY-BOCS scores, suggesting that concurrent changes in depressive symptoms were unlikely to have driven the reported results.

Discussion

In this study, three distinct observations were made: (i) the SSRI sertraline and specific cognitive behavior therapy markedly reduce obsessive compulsive symptoms, (ii) this effect, though robust and significant, seldom does achieve full remission, and (iii) this effect is associated with a significant pre–post increase in whole-brain 5-HT synthesis capacity in those patients who respond to either treatment. Moreover, in the whole patient sample, increases in global 5-HT synthesis capacity correlated with reductions in OCD symptom severity. Regional changes in absolute α-[^{11}C]MTrp trapping also revealed widespread increases in 5-HT synthesis capacity in responders and partial responders to either CBT or SSRI treatment (Supplementary Figure 1). Collectively, these findings support a primarily brain-wide, rather than localized, enhancement of central 5-HT synthesis capacity during effective cognitive-behavioral or sertraline (SSRI) treatment in OCD.

The reductions in obsessive-compulsive symptoms observed here are in line with previous reports of SSRI or CBT efficacy in OCD patients[1,2]. However, whereas seven patients achieved symptom remission, as defined by a Y-BOCS score ≤ 12[39], nine patients did not remit following 12 weeks of conventional treatment. A greater understanding of the mechanisms that support symptom reduction is critical to treatment optimization, the ultimate goal being to leverage these mechanisms to achieve higher rates of remission in OCD patients. To this end, the current study emphasizes the importance of functional changes to brain 5-HT neurotransmission in the control of obsessive-compulsive symptoms, likely in conjunction with other neurotransmitters.

Independent of treatment modality, greater improvement in OCD symptoms with SSRI or CBT was also associated with higher pre-treatment 5-HT synthesis

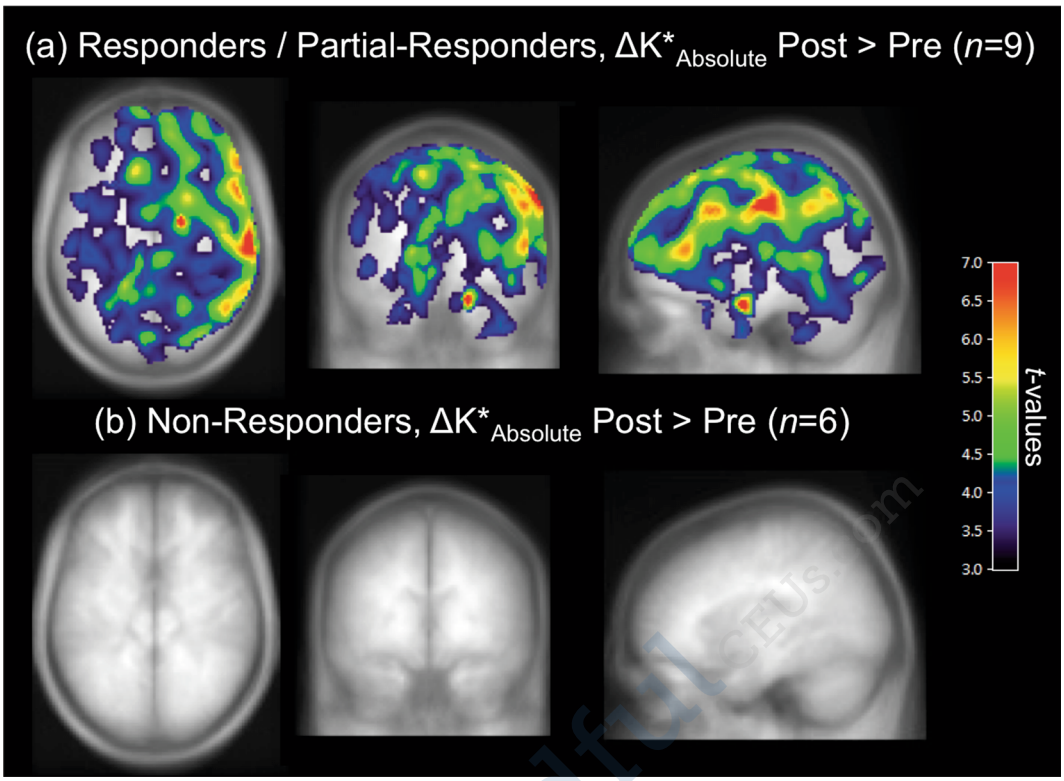


Fig. 2 Pre–post treatment increases in serotonin synthesis capacity in responders/partial responders and non-responders. Maximum intensity projections of the *t*-values, showing brain regions where absolute *K** values ($K^*_{Absolute}$) were higher post-treatment compared to pre-treatment in clinical response sub-groups. **a** Responders and partial responders to either CBT or SSRI treatment ($n = 9$) demonstrated widespread pre–post treatment increases in absolute regional *K** values. **b** Non-responders ($n = 6$) did not show any significant pre–post changes in absolute regional *K** values. For visualization purposes, the displayed *t*-map threshold was $T_8 = 3.4$ for responders/partial responders and $T_5 = 4.0$ for non-responders, with $p = 0.005$ and an extent threshold of 50 voxels

capacity in the raphe nuclei. The dorsal and median raphe nuclei are midbrain structures that contain the major serotonergic populations[40]. 5-HT is produced by the raphe nuclei, and ascending serotonergic projections from the dorsal/median raphe project to most of the brain[41], including CSTC circuitry implicated in OCD neuropathology. The observed correlation between clinical response and baseline 5-HT neurotransmission therefore prompts speculation that elevated 5-HT synthesis capacity in the raphe nuclei prior to treatment facilitates

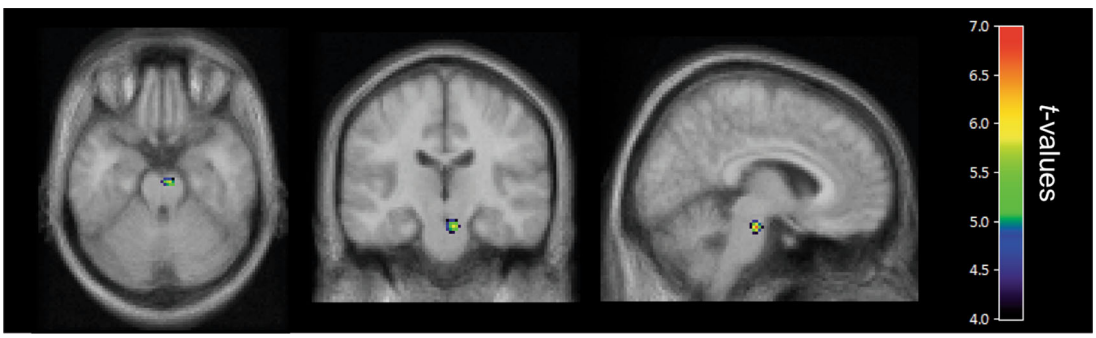


Fig. 3 Positive correlation between baseline *K values and OCD symptom improvement.** Statistical parametric maps (SPM12), with an anatomical MRI overlay, demonstrating brain regions where pre-treatment *K** values correlated positively with ΔY-BOCS in the whole sample of OCD patients ($n = 15$). The *t*-map threshold was 3.85, with $p = 0.001$ and an extent threshold of 50 voxels. A significant cluster was found in the right rostral raphe nuclei ($t_{13} = 6.66$, $k = 67$ voxels, coordinates $x, y, z = 6, -20, -22$ mm)

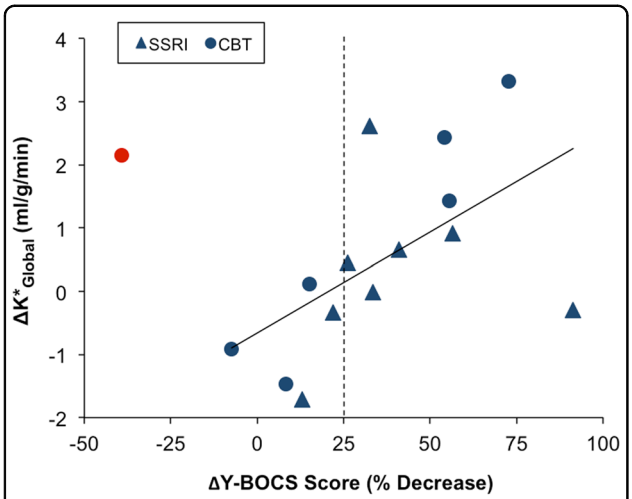


Fig. 4 Changes in global *K values vs. changes in OCD symptom severity.** Pre–post treatment changes in global *K** values (ΔK^*_{global}) correlated positively with % decrease in Y-BOCS scores ($r_s = 0.46$, $p = 0.08$). Notably, there was a clear outlier in this correlation (with the outlier removed, $r_s = 0.67$, $p = 0.009$); the outlier (red circle) was not included in the least-squares linear fit to the data shown here. Patients treated with sertraline are represented by triangles, and patients treated with CBT are represented by circles. The ΔY-BOCS score cut-off for responder/partial responder and non-responder subgroups is indicated with the dashed vertical line. Y-BOCS Yale-Brown Obsessive-Compulsive Scale, r_s Spearman's rank correlation coefficient

increases in the terminal regions during clinical improvement.

Taken together with our previous findings of abnormally elevated brain regional 5-HT synthesis capacity in OCD patients at baseline[25], the results presented here provide preliminary support for a serotonergic "braking system" operative during successful *therapeutics* in OCD. The current observations of further increases in 5-HT synthesis capacity with effective treatment support a *compensatory*, rather than pathological, role of 5-HT neurotransmission in OCD. The serotonergic braking system model posits that activation of the central serotonergic system, prior to treatment, might connote an *unsuccessful attempt* to inhibit obsessive-compulsive symptoms. CBT or SSRI exposure in OCD patients that respond to treatment could enhance this pre-existing serotonergic braking system, such that it can more effectively inhibit OC symptoms. Considering the observed association between higher pre-treatment 5-HT synthesis capacity in the raphe nuclei and greater clinical response, standard OCD treatments may provide sufficient support to this braking system in patients with higher serotonergic functioning at baseline, therefore enabling a therapeutic response. In line with the present findings, long-term treatment with SSRIs has been found to increase serotonergic neurotransmission in animals[42–44], and, more specifically, long-term administration of sertraline has been shown to increase 5-HT synthesis in the dorsal raphe nucleus of the rat[45]. Furthermore, as reductions in brain 5-HTT expression are associated with increased serotonergic neurotransmission[46,47], findings of reduced 5-HTT availability in OCD patients at baseline, and further reductions in 5-HTT availability with clomipramine or escitalopram treatment[17,48], are also consistent with a serotonergic braking system.

In psychiatry, it is often assumed that abnormal brain processes will normalize to those of healthy controls with successful treatment; for example, in depression, 5-HT metabolism has been shown to be abnormally low at baseline[24] and to normalize (increase) with antidepressant treatment[49]. Earlier brain functional imaging studies of OCD patients have also demonstrated normalization (via reduction) of glucose metabolism in OCD patients who respond to either behavioral or drug therapy[6,7]. These findings are not necessarily incongruous with the current 5-HT metabolism observations; for example, pharmacological manipulations that decrease glucose metabolism have been associated with increases in 5-HT metabolism in rodents[50]. Alternatively, the link between previous glucose metabolism findings and the current 5-HT metabolism findings in OCD could be mediated by other neural mechanisms and neurotransmitters.

Indeed, neurotransmitters seldom act in isolation. Other mechanisms and neurotransmitters, including dopamine and glutamate, have been implicated in OCD[51,52], and likely interact with the serotonergic system in OCD[11,53,54]. Dopamine, for example, is also an important neurotransmitter in the CSTC circuit, and hyperactive dopaminergic functioning within the striatum has been associated with OCD[11] and with compulsive behaviors in animal models of OCD[55]. Although the serotonergic findings reported here were brain-wide, our ROI analyses revealed significant increases in 5-HT synthesis capacity within CSTC circuitry following successful treatment, including in the bilateral caudate (see Supplementary Figure 1). It is possible that the 5-HT braking system counteracts dopaminergic hyperactivity within CSTC circuitry through serotonin–dopamine interactions. Specifically, increased 5-HT synthesis capacity associated with successful CBT or SSRI treatment may result in augmented 5-HT tonic inhibition of dopamine activity, and thus a reduction in compulsive symptoms. Accordingly, clinical response to SSRI therapy in OCD has been associated with reduced dopaminergic activity in the basal ganglia[56], and can be improved using dopamine antagonist augmentation strategies[57]. Another potential mechanism underlying the observed link between elevated 5-HT metabolism and greater therapeutic response could be the known trophic properties of 5-HT in the regulation of cell proliferation, differentiation, and maturation[58]. In support of a potential

neurogenic mechanism mediating the relationship between 5HT metabolism and effective treatment, 5-HT1A receptor knockout mice showed impaired neurogenesis and were insensitive to the behavioral effects of the SSRI fluoxetine[59]. It is also conceivable that non-response to SSRI or CBT may invoke mechanisms and/or neuromodulators other than serotonin. In such treatment-refractory patients, alternative therapies such as deep brain stimulation[60] or SSRI augmentation with an antipsychotic[57] might be beneficial.

Some limitations of the current study should be considered. (I) Although well within the range of similar studies in the field, the sample size is modest, thus replication of these findings is critical. (II) OCD research is often confounded by clinical and biological hetero-geneity. Here, considerable attention was focused on preventing contamination of the biological measure of interest by non-specific factors; yet, controlling for all the non-specific factors, known (sleep, mood, motor activity, biological rhythms) or not yet known, is always difficult in clinical behavioral research, in particular with widespread neurotransmitters, such as serotonin. (III) Patients with OCD may require longer-term treatment with specialty CBT in order to optimize treatment response (see Sookman[27] for review). Important differences in clinical and physiological indices between the treatment groups may have emerged following longer treatment duration. (IV) Several patients had been previously treated with SSRIs and/or behavioral therapy, although these patients were free of treatment for 3–90 months prior to beginning the study. Thus, we cannot formally exclude the possibility that some of the observed modifications after CBT or SSRI treatment were facilitated by previous treatments.

(V) The significance of the α-[^{11}C]MTrp/PET method has been discussed in some detail, and it has been suggested that the method might measure the blood–brain barrier transport of tryptophan rather than the synthesis of serotonin[61]. These reservations have been addressed in several studies and reviews from our group[19,32,33,62–65] and others[20,66,67], and cross-validation studies support the general consensus that brain regional α-[^{11}C]MTrp trapping provides an acceptable proxy for 5-HT synthesis. (VI) It is unlikely that the observed pre–post treatment differences in regional K^* values could be attributed to changes in cerebral blood flow due to treatment, since tracers with a low plasma–brain rate constant, such as α-[^{11}C]MTrp, are insensitive to variations in cerebral blood flow[68].

In conclusion, the present study did not identify region-specific changes in 5-HT synthesis capacity following treatment with either sertraline or CBT for OCD. Yet, the evidence that elevations in brain-wide serotonergic function co-varied with clinical response raises the intriguing possibility that these increases in OCD are *compensatory*. In this model, a serotonergic braking system, which is unable to sufficiently inhibit dysfunctional mechanisms prior to treatment, could become *more* engaged over the course of successful treatment with either SSRI or CBT in OCD, allowing OCD symptoms to be more effectively controlled.

Conflict of interest

The authors declare that they have no conflict of interest

References

1. Öst, L.-G., Havnen, A., Hansen, B. & Kvale, G. Cognitive behavioral treatments of obsessive–compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014. *Clin. Psychol. Rev.* **40**, 156–169 (2015).
2. Bloch, M. H., McGuire, J., Landeros-Weisenberger, A., Leckman, J. F. & Pittenger, C. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. *Mol. Psychiatry* **15**, 850–855 (2010).
3. Benkelfat, C. et al. Clomipramine in obsessive-compulsive disorder: further evidence for a serotonergic mechanism of action. *Arch. Gen. Psychiatry* **46**, 23 (1989).
4. Murphy, D. L., Pato, M. T. & Pigott, T. A. Obsessive-compulsive disorder: treatment with serotonin-selective uptake inhibitors, azapirones, and other agents. *J. Clin. Psychopharmacol.* **10**, 91S–100S (1990).
5. Aouizerate, B. et al. Pathophysiology of obsessive-compulsive disorder: a necessary link between phenomenology, neuropsychology, imagery and physiology. *Prog. Neurobiol.* **72**, 195–221 (2004).
6. Benkelfat, C. et al. Local cerebral glucose metabolic rates in obsessive-compulsive disorder: patients treated with clomipramine. *Arch. Gen. Psychiatry* **47**, 840–848 (1990).
7. Baxter, L. R. et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch. Gen. Psychiatry* **49**, 681–689 (1992).

8. Apostolova, I. et al. Effects of behavioral therapy or pharmacotherapy on brain glucose metabolism in subjects with obsessive-compulsive disorder as assessed by brain FDG PET. *Psychiatry Res.* **184**, 105–116 (2010).
9. Stengler-Wenzke, K., Müller, U., Angermeyer, M. C., Sabri, O. & Hesse, S. Reduced serotonin transporter-availability in obsessive-compulsive disorder (OCD). *Eur. Arch. Psychiatry Clin. Neurosci.* **254**, 252–255 (2004).
10. Matsumoto, R. et al. Reduced serotonin transporter binding in the insular cortex in patients with obsessive-compulsive disorder: a [11C]DASB PET study. *Neuroimage* **49**, 121–126 (2010).
11. Perani, D. et al. In vivo PET study of 5HT2A serotonin and D2 dopamine dysfunction in drug-naive obsessive-compulsive disorder. *Neuroimage* **42**, 306–314 (2008).
12. Pogarell, O. et al. Elevated brain serotonin transporter availability in patients with obsessive-compulsive disorder. *Biol. Psychiatry* **54**, 1406–1413 (2003).
13. Simpson, H. B. et al. Serotonin transporters in obsessive-compulsive disorder: a positron emission tomography study with [(11)C]McN 5652. *Biol. Psychiatry* **54**, 1414–1421 (2003).
14. Simpson, H. B. et al. Serotonin 2A receptors in obsessive-compulsive disorder: a positron emission tomography study with [11C]MDL 100907. *Biol. Psychiatry* **70**, 897–904 (2011).
15. Thorén, P. et al. Clomipramine treatment of obsessive-compulsive disorder: II. Biochemical aspects. *Arch. Gen. Psychiatry* **37**, 1289–1294 (1980).
16. Insel, T. R., Mueller, E. A., Alterman, I., Linnoila, M. & Murphy, D. L. Obsessive-compulsive disorder and serotonin: is there a connection? *Biol. Psychiatry* **20**, 1174–1188 (1985).
17. Zitterl, W. et al. Changes in thalamus-hypothalamus serotonin transporter availability during clomipramine administration in patients with obsessive-compulsive disorder. *Neuropsychopharmacology* **33**, 3126–3134 (2008).
18. Descarries, L., Soucy, J. P., Laeaille, F., Mrini, A. & Tanguay, R. Evaluation of three transporter ligands as quantitative markers of serotonin innervation density in rat brain. *Synapse* **21**, 131–139 (1995).
19. Diksic, M. & Young, S. N. Study of the brain serotonergic system with labeled α-methyl-L-tryptophan. *J. Neurochem.* **78**, 1185–1200 (2001).
20. Chugani, D. C. & Muzik, O. α[C-11]methyl-L-tryptophan PET maps brain serotonin synthesis and kynurenine pathway metabolism. *J. Cereb. Blood. Flow. Metab.* **20**, 2–9 (2000).
21. Diksic, M., Nagahiro, S., Sourkes, T. L. & Yamamoto, Y. L. A new method to measure brain serotonin synthesis in vivo. I. Theory and basic data for a biological model. *J. Cereb. Blood Flow Metab.* **10**, 1–12 (1990).
22. Chugani, D. C. et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann. Neurol.* **45**, 287–295 (2001).
23. Leyton, M. et al. Brain regional α-[^{11}C]methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *Am. J. Psychiatry* **158**, 775–782 (2001).
24. Rosa-Neto, P. et al. Measurement of brain regional α-[^{11}C]methyl-L-tryptophan trapping as a measure of serotonin synthesis in medication-free patients with major depression. *Arch. Gen. Psychiatry* **61**, 556–563 (2004).
25. Berney, A. et al. Brain regional α-[^{11}C]methyl-L-tryptophan trapping in medication-free patients with obsessive-compulsive disorder. *Arch. Gen. Psychiatry* **68**, 732–741 (2011).
26. First, M. B., Spitzer, R. L., Gibbon, M. & Williams, J. B. Structured clinical interview for DSM-IV axis I disorders (SCID I/P, Version2.0). 1995.
27. Sookman, D. *Specialized Cognitive Behavior Therapy for Obsessive Compulsive Disorder: An Expert Clinician Guidebook*. (Routledge, New York (NY), 2016).
28. Fernstrom, J. D. et al. Diurnal variations in plasma concentrations of tryptophan, tryosine, and other neutral amino acids: effect of dietary protein intake. *Am. J. Clin. Nutr.* **32**, 1912–1922 (1979).
29. Maswood, S., Truitt, W., Hotema, M., Caldarola-Pastuszka, M. & Uphouse, L. Estrous cycle modulation of extracellular serotonin in mediobasal hypothalamus: role of the serotonin transporter and terminal autoreceptors. *Brain. Res.* **831**, 146–154 (1999).
30. Jovanovic, H. et al. PET study of 5-HT_{1A} receptors at different phases of the menstrual cycle in women with premenstrual dysphoria. *Psychiatry Res. Neuroimaging* **148**, 185–193 (2006).
31. Mzengeza, S., Venkatachalam, T. K. & Diksic, M. Asymmetric radiosynthesis of α-[^{11}C]methyl-L-tryptophan for PET studies. *Nucl. Med. Biol.* **22**, 303–307 (1995).
32. Nishizawa, S. et al. Validation of a less-invasive method for measurement of serotonin synthesis rate with α-[^{11}C]methyl-tryptophan. *J. Cereb. Blood. Flow. Metab.* **18**, 1121–1129 (1998).
33. Okazawa, H., Leyton, M., Benkelfat, C., Mzengeza, S. & Diksic, M. Statistical mapping analysis of serotonin synthesis images generated in healthy volunteers using positron-emission tomography and α-[^{11}C]methyl-L-tryptophan. *J. Psychiatry Neurosci.* **25**, 359–370 (2000).
34. Patlak, C. S., Blasberg, R. G. & Fenstermacher, J. D. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J. Cereb. Blood Flow Metab.* **3**, 1–7 (1983).
35. Rosa-Neto, P., Diksic, M., Leyton, M., Mzengeza, S. & Benkelfat, C. Stability of α-[^{11}C]methyl-L-tryptophan brain trapping in healthy male volunteers. *Eur. J. Nucl. Med. Mol. Imaging* **32**, 1199–1204 (2005).
36. Collins, D. L., Neelin, P., Peters, T. M. & Evans, A. C. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* **18**, 192–205 (1994).
37. Collins, D. L. & Evans, A. C. Animal: validation and applications of nonlinear registration-based segmentation. *Int. J. Pattern Recogn.* **11**, 1271–1294 (1997).
38. Collins, D. L, Zijdenbos, A. P., Baaré, W. F. & Evans, A. C. ANIMAL+INSECT: improved cortical structure segmentation. In *Information Processing in Medical Imaging. IPMI 1999. Lecture Notes in Computer Science*, Vol. 1613 (eds. Kuba, A., Šáamal, M. & Todd-Pokropek, A.) 210–223 (Springer, Berlin, Heidelberg, 1999).
39. Mataix-Cols, D. et al. Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. *World Psychiatry* **15**, 80–81 (2016).
40. Dahlström, A. & Fuxe, K. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand. Suppl.* **232**, 1–55 (1964).
41. Azmitia, E. C. & Segal, M. An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *J. Comp. Neurol.* **179**, 641–667 (1978).
42. Chaput, Y., de Montigny, C. & Blier, P. Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments: an in vivo electrophysiologic study in the rat. *Neuropsychopharmacology* **5**, 219–229 (1991).
43. Briley, M. & Moret, C. Neurobiological mechanisms involved in antidepressant therapies. *Clin. Neuropharmacol.* **16**, 387–400 (1993).
44. El Mansari, M., Bouchard, C. & Blier, P. Alteration of serotonin release in the guinea pig orbito-frontal cortex by selective serotonin reuptake inhibitors: relevance to treatment of obsessive-compulsive disorder. *Neuropsychopharmacology* **13**, 117–127 (1995).
45. Kim, S. W., Park, S. Y. & Hwang, O. Up-regulation of tryptophan hydroxylase expression and serotonin synthesis by sertraline. *Mol. Pharmacol.* **61**, 778–785 (2002).
46. Mathews, T. A. et al. Gene dose-dependent alterations in extraneuronal serotonin but not dopamine in mice with reduced serotonin transporter expression. *J. Neurosci. Methods* **140**, 169–181 (2004).
47. Zhao, Z., Zhang, H.-T., Bootzin, E., Millan, M. J. & O'Donnell, J. M. Association of changes in norepinephrine and serotonin transporter expression with the long-term behavioral effects of antidepressant drugs. *Neuropsychopharmacology* **34**, 1467–1481 (2008).
48. Kim, E. et al. Altered serotonin transporter binding potential in patients with obsessive-compulsive disorder under escitalopram treatment: [^{11}C]DASB PET study. *Psychol. Med.* **46**, 357–366 (2016).
49. Berney, A. et al. An index of 5-HT synthesis changes during early antidepressant treatment: α-[11C]methyl-l-tryptophan PET study. *Neurochem. Int.* **52**, 701–708 (2008).
50. Vahabzadeh, A., Boutelle, M. G. & Fillenz, M. Effects of changes in rat brain glucose on serotonergic and noradrenergic neurons. *Eur. J. Neurosci.* **7**, 175–179 (1995).
51. Denys, D., Zohar, J. & Westenberg, H. G. The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. *J. Clin. Psychiatry* **65**, 11–17 (2004).
52. Wu, K., Hanna, G. L., Rosenberg, D. R. & Arnold, P. D. The role of glutamate signaling in the pathogenesis and treatment of obsessive–compulsive disorder. *Pharmacol. Biochem. Behav.* **100**, 726–735 (2012).
53. Goodman, W. K., McDougle, C. J., Price, L. H. & Riddle, M. A. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder?. *J. Clin. Psychiatry* **51**(Suppl.), 36–43 (1990).
54. Sasaki-Adams, D. M. & Kelley, A. E. Serotonin-dopamine interactions in the control of conditioned reinforcement and motor behavior. *Neuropsychopharmacology* **25**, 440–452 (2001).
55. Berridge, K. C., Aldridge, J. W., Houchard, K. R. & Zhuang, X. Sequential superstereotypy of an instinctive fixed action pattern in hyper-dopaminergic

mutant mice: a model of obsessive compulsive disorder and Tourette's. *BMC Biol.* **3**, 4 (2005).
56. Moresco, R. M. et al. Fluvoxamine treatment and D_2 receptors: a PET study on OCD drug-naïve patients. *Neuropsychopharmacology* **32**, 197–205 (2007).
57. Dold, M., Aigner, M., Lanzenberger, R. & Kasper, S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *Int. J. Neuropsychopharmacol.* **16**, 557–574 (2013).
58. Azmitia, E. C. Modern views on an ancient chemical: serotonin effects on cell proliferation, maturation, and apoptosis. *Brain Res. Bull.* **56**, 413–424 (2001).
59. Santarelli, L. et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301**, 805–809 (2003).
60. Alonso, P. et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PLoS ONE* **10**, e0133591 (2015).
61. Shoaf, S. E. et al. The suitability of [^{11}C]-α-methyl-L-tryptophan as a tracer for serotonin synthesis: studies with dual administration of [^{11}C] and [^{14}C] labeled tracer. *J. Cereb. Blood Flow Metab.* **20**, 244–252 (2000).
62. Leyton, M., Diksic, M. & Benkelfat, C. Brain regional α-[^{11}C]methyl-L-tryptophan trapping correlates with post-mortem tissue serotonin content and [^{11}C]5-hydroxytryptophan accumulation. *Int. J. Neuropsychopharmacol.* **8**, 1–2 (2005).
63. Diksic, M., Tohyama, Y. & Takada, A. Brain net unidirectional uptake of α-[14C] methyl-L-tryptophan (α-MTrp) and its correlation with regional serotonin synthesis, tryptophan incorporation into proteins, and permeability surface area products of tryptophan and α-MTrp. *Neurochem. Res.* **25**, 1537–1546 (2000).
64. Diksic, M. Labelled (alpha)-methyl-L-tryptophan as a tracer for the study of the brain serotonergic system. *J. Psychiatry Neurosci.* **26**, 293 (2001).
65. Tohyama, Y., Takahashi, S., Merid, M. F., Watanabe, A. & Diksic, M. The inhibition of tryptophan hydroxylase, not protein synthesis, reduces the brain trapping of α-methyl-L-tryptophan: an autoradiographic study. *Neurochem. Int.* **40**, 603–610 (2002).
66. Muzik, O., Chugani, D. C., Chakraborty, P., Mangner, T. & Chugani, H. T. Analysis of [C-11]alpha-methyl-tryptophan kinetics for the estimation of serotonin synthesis rate in vivo. *J. Cereb. Blood Flow Metab.* **17**, 659–669 (1997).
67. Chugani, D. C. & Chugani, H. T. PET: mapping of serotonin synthesis. *Adv. Neurol.* **83**, 165–171 (2000).
68. Fenstermacher, J. D., Blasberg, R. G. & Patlak, C. S. Methods for quantifying the transport of drugs across brain barrier systems. *Pharmacol. Ther.* **14**, 217–248 (1981).

BMJ Open

Brief strategic therapy for obsessive–compulsive disorder: a clinical and research protocol of a one-group observational study

ABSTRACT

Introduction: Obsessive–compulsive disorder (OCD) is a disabling psychopathology. The mainstay of treatment includes cognitive–behavioural therapy (CBT) and medication management. However, individual suffering, functional impairments as well as the direct and indirect costs associated with the disease remain substantial. New treatment programmes are necessary and the brief strategic therapy (BST) has recently shown encouraging results in clinical practice but no quantitative study has as yet been conducted.

Methods and analysis: The clinical effectiveness of the OCD-specific BST protocol will be evaluated in a one-group observational study. Participants will be sequentially recruited from a state community psychotherapy clinic in Dublin, Ireland. Outcome measures will be the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Beck Depression Inventory-II (BDI-II). Data will be collected at baseline, at treatment termination and at 3 month follow-up. The statistical significance of the post-treatment effect will be assessed by the paired-sample Student t test, while clinical significance will be evaluated by means of the equivalence testing method, which will be also used to assess the maintenance of effect at follow-up.

Ethics/dissemination: The present study is approved by the Hesed House Ethics Board in Dublin. Findings will enhance the evidence-based knowledge about the clinical effectiveness of BST in treating OCD symptoms, prior to assessing its efficacy in a randomised and controlled clinical trial, and will be disseminated through publication in peer-reviewed journals and conference presentations.

Strengths and limitations of this study

- The observational study design allows the assessment of treatment effects in real-world settings.
- A positive result in an observational study can inform practice directly.
- The lack of a concurrent control group limits the internal validity of results.
- A convenience sampling limits the generalisability of results.

INTRODUCTION

Obsessive–compulsive disorder (OCD) is an anxiety syndrome characterised by the presence of recurrent or persistent thoughts, impulses or images (obsessions) that are experienced as intrusive or distressing by the person, and that he or she attempts to ignore or suppress by performing repetitive behaviours or mental acts (compulsions).[1] Symptoms usually begin gradually, tend to vary in severity throughout the individual's life, and generally worsen when intense stress is experienced by the person. OCD, considered a lifelong disorder, can be so severe and time-consuming to the point of significantly interfering with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.[2] Epidemiological studies report a lifetime disorder's prevalence of 1–4% in the general population,[3–5] equal for men and women, although it is more commonly diagnosed among boys than girls.[4 6] The Global Burden of Diseases study has recently ranked OCD as the 10th leading cause of disability worldwide[7] and it is also considered the fourth most common mental illness in many western countries.

Most adults recognise that their obsessions and compulsions do not make sense, but that is not always the case. In addition, children may not realise that something is wrong, and too often even healthcare professionals do not identify the need for appropriate interventions,[8] contributing to make OCD a very difficult-to-treat disorder. Sufferers of OCD generally display many non-OCD symptoms, such as signs of

depression,[9] excessive worry, extreme tension[10] as well as severe occupational, social and family dysfunction.[4 11 12] Aside from the compulsive behaviours, there are no physical symptoms of OCD; however, OCD sufferers can develop physical problems. For example, in the presence of germ obsession, they may wash their hands so much as to make their skin red, raw and painful.

Most people with OCD fall into the *washers* category. They are afraid of contamination and usually have cleaning or hand-washing compulsions. *Checkers*, instead, repeatedly check things (oven turned off, door locked, etc) that they associate with harm or danger, and *hoarders* fear that something bad will happen if they throw anything away. They compulsively hoard things that they do not need or use. Another OCD pattern is the pathological doubt that if everything is not perfect or done just right, something terrible will happen, or they will be punished (*doubters* and *sinners*). *Counters* and *arrangers*, in addition, are obsessed with order and symmetry and they may have superstitions about certain numbers, colours or arrangements.

Most people with OCD present with both obsessions and compulsions, but some persons may experience just one or the other. OCD symptoms manifestation also vary greatly from individual to individual, and access to flexible, innovative, affordable and evidence-based psychological treatments for OCD is required.

Current treatments for OCD

There are different ways to treat OCD. These include psychotherapies, drugs (antidepressants) or a combination of both.

Cognitive–behavioural therapy (CBT) combined with antidepressant medication currently represents the best treatment option for OCD.[13] This blended intervention does not provide a 'cure' for OCD, but controls the symptoms and enables people with OCD to restore normal functioning in their lives.

CBT refers to two distinct treatments: exposure and response prevention (ERP) therapy and cognitive therapy (CT).[14] Although these treatments are increasingly offered in combination, they will be discussed separately.

Before starting ERP treatment, patients make a 'hierarchy' of situations that provoke in them obsessional fears; then they participate in exposure tasks, and subsequently they are asked to pay particular attention to thoughts and feelings related to these situations.[15]

ERP treatment involves a direct or imagined, controlled exposure to objects or situations that cause the patient mild-to-moderate anxiety. Over time, exposure to obsessional cues helps the individual to gradually 'get used' to (or habituated) to them, leading to reduction in anxiety. Exposure tasks are generally first performed with the therapist assisting, and sessions usually take between 45 min and 3 h. Patients are also asked to practise exposure tasks between sessions for 2–3 h/day.

The main goal during both in vivo and imagery exposure is essentially for the person to stay in contact with the obsessional trigger without engaging in ritual behaviours,[16–18] and the treatment duration depends on the patient's ability to tolerate anxiety and to resist compulsive behaviours.[19]

CT is focused instead on how participants interpret their obsessions: what they believe or assume to be true about them, what their attitude is towards them and why they think they have these obsessions. It is essentially aimed at helping participants to identify and re-evaluate beliefs about the potential consequences of engaging or not engaging in compulsive behaviour, so as to address it.

CBT, particularly ERP, was found to be effective in a number of clinical trials.[4] Findings have shown CBT as being able to address OCD symptoms more than pharmacotherapy and to guarantee good follow-up rates of success among respondents.[4 6] Notably, despite showing lower relapse rates than pharmacotherapy (12% vs 24–89%), for its own nature CBT causes people anxiety, and about 25% of patients drop out before termination or refuse the treatment.[4 12] Specifically, patients presenting with more obsessions than compulsions may confront serious difficulties with CBT, since some techniques can maintain the obsessions by turning the attention of the individual to the preoccupations themselves.[6 20]

Studies documenting the benefits of ERP have found that 75% of respondents experience enhancement in OCD symptoms during the treatment, the majority of them showing continuous improvements even after 3 years from the end of the intervention. However, only 25–40% of patients reach full recovery, while most of them remain long-term symptomatic.[21] The main reasons for failure of CBT include patients' lack of motivation in reducing rituals and the presence of comorbid disorders, such as moderate-to-severe depression or avoidant personality disorder.[22] Unfortunately, even with effective medication, responders who suffer from severe symptoms show residual impairments[9] and there are also serious health concerns with long-term pharmacotherapy usage.

At present, no treatment has been demonstrated to be totally curative for OCD. Most interventions can be expected to reduce symptoms by 50–80%. However, the illness is cyclic, and worsens when the individual is under stress. Additional treatment strategies are thus required to more effectively tailor this complex symptomatology.

The advanced model of brief strategic therapy (BST)

According to the Brief Strategic treatment for OCD, if the disorder is not completely 'solved', symptoms tend to reoccur, and empirical evidence shows BST as being particularly effective in guaranteeing long-term stability of therapeutic outcomes.[23]

Clinical evidence demonstrates that BST is effective in treating several forms of psychological suffering, including OCD. The Brief Strategic approach makes a self-corrective operative diagnosis of a problem, which means that theoretical knowledge of OCD can be achieved only after a series of solution-based strategies have been applied, resulting effectively in addressing the symptoms. In other words, *knowing a reality through the strategies that can change it*. The fundamental concept of BST is that when a problem or difficulty arises, patients try to solve it, either relying on past experiences by reapplying solutions that have been successful in solving a similar situation in the past, or by attempting new strategies. If these expedients do not work, rather than making use of alternative solutions, the natural tendency is to reiterate them, giving rise to a complex process of retroactions which maintain or exacerbate, instead of modify, the problematic situation. So, the 'attempted solutions' themselves become a problem. Thus, psychological problems are the result of a dysfunctional or pathogenic *perceptive–reactive system*,[23] defined as a 'redundant modality through which a given individual perceives and consequently reacts to his own reality in relationship with himself, with others, and with the world' (ref. 24, p. 23).

The strategic psychotherapist is not interested in discovering why a problem exists, but *how it is maintained in the present*, promoting therapeutic change by applying specific intervention strategies.[25] Strategic protocols represent rigorous sequences of therapeutic manoeuvres with heuristic and predictive power. Like a game of chess, the therapy becomes a process of strategic problem solving where the experienced players always keep in mind which strategy will lead to a checkmate as he responds to the adversary's moves. The potential reaction to each manoeuvre is predicted and strategical are changes planned on the basis of the observed effects through an ongoing self-corrective process. Since every human interaction, including the therapeutic one, is meant to be unique and unrepeatable, the BST therapist continuously adapts his or her logic and language to those of the patient, promoting flexible, individually tailored interventions.[26]

The metaphorical image that best represents the underlying logic of OCD is made from a story by Paul Watzlawick: 'A man claps his hands every ten seconds. Asked about the reason for this strange behavior, he explains: "in order to scare away the elephants.' When told there are no elephants present, the man responds: 'well, there you go. See?'". The typical perceptive–reactive system of patients with OCD may be fear or pleasure based. Obsessive ideas emerge as often unreasonable repetitive fixations from which individuals cannot free themselves without performing specific compulsive thinking, formulas or ritual actions.[11 27] However, the attempt to take the matter in hand themselves leads the person to lose control over the situation, and compulsions become inevitable.[11] It is healthy, for example, to be careful not to get dirty and maintain oneself clean, but it is insane to wash for hours and hours and still doubting that it is not enough. Or, before going to bed, it is certainly a good habit to check that doors, taps or gas valves are closed, but it is definitely absurd to return home or wake up several times during the night for further control. It can also be considered appropriate to take measures in order to pass an exam or to face a stressful situation, but it becomes dysfunctional to structure propitiatory rituals without which it is unthinkable to deal with the circumstance. As Samuel Johnson states (1709–1784): 'the chains of habit are too weak to be felt until they are too strong to be broken', and patients with OCD, notoriously resistant to change, usually ask for help when they lose power over their own actions and thoughts and the problem becomes so much diffused as to affect most aspects of their life. Compulsions, of their own nature, are not illogical, and rationalistic explanations do not lead to any therapeutic success. The use of a non-ordinary logic (opposed to the traditional, rationalistic Aristotelian model) then becomes necessary in order to reorient the symptom towards its self-annulment. First, it is conveyed to patients that what they think and do makes sense; they are given the illusion that the therapist knows a more functional way to manage the situation. In other words, the BST professional needs to follow the logic that underlies the patient's ideas and actions.[28]

Nardone and Portelli[11] defined five reasons that trigger compulsive thoughts and actions: (1) the turning up of a *doubt generating the need for reassuring answers*; (2) an *excess of ideological rigidity* as well as extreme *moral respect or religious belief*; (3) the *excess of rational reasoning processes*, until they become completely unreasonable; (4) an *extreme health prevention* that becomes a phobia and (5) the attempt of reducing anxiety and distress generated by a *trauma*. For each of these reasons, the purpose may be to *prevent* or *repair* something that 'might' happen or 'has' happened, respectively, as well as to *propitiate* or ensure that things continue to go well.

After having discriminated whether the compulsion is phobic or non-phobic based, in order to achieve the pragmatic knowledge of how to build a successful therapeutic intervention, the Brief Strategic model focuses on the patient's attempted solutions, which in the case of a person suffering from OCD are typically represented by: (1) avoidance of situations that cause anxiety; (2) request for help, reassurance or protection from others in the form of delegation of tasks or in seeking assistance for avoiding contact with fearful stimuli and (3) control of anxiety-laden situations through performing rituals: preventive, propitiatory and reparatory. Other important discriminations to be made are: (1) whether the compulsion is represented by repetitive visible actions or remains at a mental level and (2) if the ritual follows a specific sequence, either numerical or analogical (figure 1).

Perceptive-reactive system – compulsion		
Phobic - based on *fear*		Non phobic - based on *pleasure*
Involvement of others		
No		Yes
For shame or because others would not be able to adequately perform the ritual.		- Seeking assistance - Avoiding to do tasks
Reaction		
Actions		Thoughts
Typology of the ritual		
Past-oriented		Future-oriented
Propitiatory	Reparative	Preventive
Sequence of the ritual		
Yes		No
Numerical: based on quantity	Analogical: based on quality	

Figure 1 Discriminating factors of the strategic intervention.

In order to interrupt the attempted solutions which worsen the situation, the brief strategic therapist, through the use of specific therapeutic communication techniques (strategic dialogue), starts restructuring the perception of the patient's reality by the use of a direct form of communication (ie, 'the more you avoid the fearful situation, the more frightening it becomes' or 'the more you ask for help, the more incapable you become. It invalidates you more and more') aimed at instilling the doubt about the correctness of the person's thoughts and actions.

Depending on the structure of the ritual, an essential and unique aspect of BST is having devised five major techniques specifically designed to dismantle the maintenance mechanism of the symptomatology.[28] Therapeutic prescriptions or injunctions need to be implemented between sessions, in real life, so as to make the patient autonomously learn how to fight his or her obsession and to change their coping actions.[11]

1. When the ritual holds a sequence, and thus is *numerical*, the intervention proceeds to give the patient a specific numerical preset counter-ritual, which fits the particular pathological ideas and actions leading to a catastrophic change. This is the case of a person who needs to check something a number of times to ensure that it has been done correctly.
2. *Progressive violations* of the sequence of the ritual, from small to total violation, in order to break the established rigid control.
3. The technique of *postponing the ritual* to a specific and prescribed time is aimed at making boring, annoying and unpleasant the individuals' main source of pleasure or gratification, which was driven by impulses. This strategy has been proven to be particularly useful with the vomiting syndrome, a compulsion based on pleasure. Once again, the attempted solution of vomiting for weight control after having binged gradually becomes the problem, and the reason it persists lies in the pleasure provided. Since any repressing intervention would only exacerbate the desire to binge and vomit, by altering the spontaneity of the cycle, the interval technique takes away the enjoyment of the liberating act of vomiting, usually accompanied by the feeling of an almost orgasmic urgency, which progressively becomes more difficult and unpleasant. Thus, a ritual based on pleasure is transformed into an act of self-torture.
4. *Ritualising the pathological compulsion* in specific space and time sets aside during the day, first numerous then progressively reducing this ritualized ritual to 0, allows the person to take control of it, gradually demolishing the pathology.
5. Introducing '*a small disorder that maintains order*', the objective is to break the rigid control until the unstoppable need for the compulsion completely comes to a stop.

A patient who fears contamination, for example, will continuously wash, clean and sterilise himself, his house and other belongings in order to prevent being infected or contaminated. However, once this state is reached, the problem is to maintain it. In this specific case, the use of the strategic dialogue becomes necessary in order to first reframe the patient's rigid parameters, then to prepare him for complying with the idea that to be immune to dirt, he should not search for total cleanliness but should introduce 'a small disorder'. A little bit of dirt then becomes the only way to protect the person from total cleanliness, responsible for the person's increasing fear.[11] For example, while persuading a patient with OCD to stop his or her pathological rituals will not lead to any therapeutic success, a prescription based on the same logic underlying the problem will turn the force of the symptom against the disorder itself, breaking its perverse balance. If the patient is told: 'every time you enact one of your rituals, you must repeat it five times, exactly five times, no more, no less. You can avoid doing it at all, but if you do it once, you must do it no more and no less than five times', the injunction to ritually repeat the compulsive action paradoxically brings the person to build a different reality from the one characterised by uncontrollable compulsions.[23] The logical structure of this apparently simple prescription helps to 'lead the enemy go into the attic and remove the ladder': the individual is not asked to avoid executing the ritual but told, if he or she needs to perform it once, he has to do it five times. In this way, the therapist and then the patient assume control over the situation. When the patient literally follows the prescription, he or she will suspend the ritual after a few days, usually not being able to explain why. Fundamental is the way in which the prescriptions are communicated, that is, by the use of redundantly repeated hypnotic linguistic assonances and the adoption of posthypnotic messages expressed in a more marked tone of voice.

Conceptual and pragmatic comparison between CBT and BST

Similarly to CBT, BST is based on the modern *constructivist epistemology* according to which individuals actively

create their own reality in relationship with themselves, the others and the world; it also makes use of *specific treatment protocols* focused on dialogue and therapeutic prescriptions.

However, CBT derives from the learning theory, whereas the strategic approach bases its assumptions on the theory of change. In other words, while a CBT therapist guides the patient through a process of awareness and volunteer effort to learn how to fight and handle the disease, the BST professional adopts ad hoc therapeutic stratagems in order to create a corrective emotional experience in the person. By doing so, the patient's resistance to change is bypassed and the way in which they perceive and react to their own reality is transformed.

Differentiating between the two therapeutic approaches is also the type of communication and language adopted during the clinical dialogue as well as used for prescribing therapeutic injunctions. In fact, CBT is traditionally characterised by a logical–rational communication, that is, the indicative language typical of the explanation. In contrast, BST language is injunctive and performative,[29] aimed at making the person *feel* differently before acting differently through the use of metaphors, anecdotes and stories (figure 2).

STUDY AIMS AND HYPOTHESES

Since 1990, the clinical application of the BST to the treatment of OCD has been carried out at the Centro di Terapia Strategica (CTS) at Arezzo, Italy, and has progressively led to the development of ad hoc procedures that have shown to be effective in long-term case reports.[30] However, despite the encouraging clinical evidence, no quantitative study to date has assessed the effectiveness of BST for OCD.

In order to gather the first empirical evidence, the short-term and medium-term effects of BST on OCD symptoms will be investigated within a one-group observational study, a commonly used clinical and population-based research design that allows the study and the optimisation of healthcare interventions in ecological settings.[31]

Three hypotheses will be tested: (1) OCD symptoms will improve to a statistically and clinically significant extent at the end of the BST intervention; (2) the symptoms improvement will be maintained at 3 month follow-up and (3) since depressive symptoms frequently accompany OCD and appear to affect treatment outcome negatively, higher depression levels at baseline will predict lower improvements in OCD symptomatology.

METHODS

Study population and recruitment

Study participants will be recruited among the patients with OCD who are referred to the Hesed House, a state community psychotherapy clinic in Dublin, Ireland, for undertaking the BST intervention. The clinic offers state-funded treatment based on ability to pay and generally provides care to lower socioeconomic groups. Patients are referred from two general medical hospitals, the Naas General Hospital and the St James Hospital, and from a Community-based primary care Psychiatric Service, the Carlow, West Wicklow, Mental Health team, all located in Dublin, Ireland, where they undergo a diagnostic assessment and receive primary care by resident psychiatrists. On arrival at the Hesed House, patients will be consecutively screened according to the selection criteria and the eligible ones will be invited to participate in the study by a researcher who will provide them with detailed information about the study aims and procedure. Those who will agree to participate and will sign the informed consent form will be included in the study.

Inclusion and exclusion criteria

Patients will be considered eligible for the study when they meet the following *inclusion criteria*: (1) being 18 or over and (2) being assigned a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or DSM-V diagnosis of OCD by the referring psychiatrist. *Exclusion criteria* will be: (1) presenting established cognitive or communication problems which makes it challenging to understand the questionnaires and take part in the therapeutic encounters; (2) having vision impairment which makes difficult it to fill in the questionnaires and (3) suffering from other severe psychiatric disorders.

Outcome measures

The clinical severity of *OCD symptoms* will be measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),[32–34] a self-report, 10-item questionnaire extensively used in research and clinical practice to monitor improvement during treatment. The Y-BOCS consists of two parts: the Symptom Checklist for evaluating the presence of current and past symptoms, and the 10-item Severity Scale (rated 0–4 per item) that assesses obsessions and compulsions separately in five dimensions (time spent, interference, distress, resistance and control). Separate Obsession (items 1–5) and Compulsion (items 6–10) subscale scores (range 0–20) are summed to yield a total Y-BOCS score (range 0–40).[35] *Depressive symptoms* will be assessed by the Beck Depression Inventory-II (BDI-II),[36 37] a 21-question, multiple-choice, self-report inventory widely used for measuring the severity of depression.

Sample size

Twenty-eight patients at least will be included in the study. This minimum sample size was calculated considering the possible violation of the normality assumption and will give the one-tailed, non-parametric Wilcoxon signed-rank test sufficient statistical power (80%) to detect a medium-sized within-subject effect (d=0.5). If parametric assumptions will be satisfied, an equal number of participants will give the one-tailed, paired-sample Student t test a bit higher statistical power (82%)

SIMILARITIES	
• They are based on the *modern constructivist epistemology* that believes the subject being an active builder of his or her own reality and not a mere victim of it. • They make use of *specific protocols of intervention* focused on dialogue and therapeutic prescriptions. • The patient works both during the therapeutic encounters, together with the professional, and alone, between sessions. • Proven effectiveness in treating OCD in short time. • Require a good client-therapist relationship. • Emphasize collaboration and active participation. • Are focused on the present. • Sessions are structured.	
DIFFERENCES	
BST	**CBT**
Derives from the theory of change.	Derives from the theory of learning.
Represents a solution-focused approach.	Represents a problem-focused approach.
Therapist uses stratagems which create real corrective emotional experiences in the way the persons perceive and react to their own reality, leading them to acquire the skills required to autonomously cope with the situation. Change → Consciousness	Therapist guides the patient through a process based on the awareness and voluntary effort to learn how to fight or manage the disorder. Consciousness → Change
Resistances is bypassed by using stratagems that create a change beyond the voluntary effort of the patient.	Therapist goes through the willingness of the subject, often stumbles by the resistance to change which can be strong.
Methodology of research: working for effects of discovery and subsequent acquisitions.	Methodology of research: working for progressive acquisition of knowledge.
Change occurs quickly by unlocking the symptomatology in a way that may appear almost magical to the person.	Change happens gradually by helping the patients acquiring the abilities required for controlling their thoughts and actions.
Relapses are seen as opportunity to revise ongoing strategies.	Emphasizes relapse prevention.
Communication is performative and injunctive, Hypnotic and evocative language is used to makes the patient feel even before to understand. Both logic and analog languages are employed, together with suggestive metaphors as well as verbal and non-verbal hypnotic communication.	Communication is logical-rational, and make use of the indicative language typical of the explanation.
The therapist assumes a position which must be complementary to the problem of the patient to avoid in-session's confrontations, to put the patient at ease so s/he can open up, to bypass resistance, to establish therapeutic alliance, to motivate the person to do something different, and to reinforce even small successes.	The therapist assumes a direct, one-up position toward the patient.
The therapy is adapted to the patient.	The patient must follow the therapeutic rules
The therapeutic encounters can last up to 3 hours.	The therapeutic encounters do not last more than 45-60 minutes.
The patient is responsible for the success of the therapy.	The responsibility for the therapeutic success is of the therapist.

Figure 2 Comparison between CBT and BST. BST, brief strategic therapy; CBT, cognitive–behavioural therapy; OCD, obsessive–compulsive disorder.

to detect the same medium-sized within-subject effect. G*Power (V.3.1.3) was used for calculations.

Study flow

Before starting treatment, participants will be administered the study questionnaires in a quiet room under the supervision of an independent psychometrician. Treatment will take place every 2 weeks in a face-to-face setting and will consist of 10 45 min BST sessions. At the end of the last one, participants will be readministered the study questionnaires and those showing a clinically significant reduction of the Y-BOCS total score will be contacted after 3 months for the follow-up assessment, which will consist in sending the study questionnaires to participants by mail and in asking them to send them back after having answered all items. The clinical significance of the Y-BOCS total score reduction will be assessed by means of the Jacobson and Truax method.[38 39] Conversely, participants not showing a significant reduction of the Y-BOCS total score at the end of the last planned session will continue to be enrolled in the therapy and will be excluded from the follow-up study phase.

Psychotherapists and treatment fidelity

Therapists who deliver the BST treatment at the Hesed House are all trained in BST and specifically qualified for the treatment of OCD. The therapy process will be monitored and live video cases will be supervised by a BST senior clinician.

Data analysis

The one-tailed, paired-sample Student t test will be used to test the statistical significance of change in Y-BOCS scores between baseline and treatment termination. However, if data will strongly violate the parametric assumptions, then the non-parametric Wilcoxon test will be used. The second hypothesis (the maintenance of OCD symptoms improvement at the 3 month follow-up) will be tested by the equivalence testing method,[40] which will be also used to assess the clinical significance of the BST effect. This will be accomplished by determining if the study group will be equivalent to the normative sample after the BST intervention and at follow-up. Finally, the hypothesis that higher depression levels at baseline are predictive of lower reductions in OCD symptomatology at treatment termination will be tested by means of simple regression. All data analyses will be performed using SPSS V.22 (SPSS, Inc, Chicago, Illinois, USA).

Patients withdrawal and missing data analysis

Study participants may stop the treatment for any reason at any time. In addition, they may stop participating in the study and withdraw all consents. Reasons for withdrawal will be investigated and reported only for withdrawing participants giving the consent to communicate them. Missing data at treatment termination and at follow-up will be first inspected for determining the missingness pattern. Only data missing at random will be then imputed by multiple imputation.

DISSEMINATION

All participants provide written informed consent before answering the baseline questionnaires and may withdraw at any point. Findings will be published in peer-reviewed journals and presented at conferences. Authorship will follow the criteria recommended by the International Committee of Medical Journal Editors.

CONCLUSIONS

The research-intervention programme carried out for >15 years by the CTS of Arezzo, Italy, has led to the development of specific treatment protocols for a series of psychopathological disorders, and the clinical evidence that has been gathered over time supports the hypothesis that BST is highly efficacious in treating OCD. Indeed, clinical evidence shows that even the most obstinate obsessions and compulsions are usually won over by redefining the situation and by setting up a series of concrete corrective emotional experiences that free the patient from a rigid self-feeding perceptive–reactive system. Focusing on the individual attempted solutions, then understanding what maintains and worsens the problem, the strategic approach is essentially aimed at creating a corrective emotional experience, transforming the way in which the person perceives and reacts to his own reality. Through the use of ad hoc therapeutic stratagems and in-session injunctive and performative language, BST bypasses the individual usual rational mechanisms, leading to the self-destruction of the logic that imprisons the mind, then quickly interrupting the vicious cycle that maintains the problem.

Located in the tradition of Lewin, the action research method typically used for investigating the effectiveness of BST in treating diverse forms of psychopathologies refers to the long-term stability of the therapeutic outcomes, as assessed by both the therapist and the patient through a change-related rating scale, with respect to the therapeutic goal. Empirical data also refer to how many therapists apply a certain protocol in their daily practice on real patients. BST effectiveness is related to the complete extinction of the symptomatology, which is tested in follow-up encounters usually scheduled after 3, 6, 9 and 12 months after the treatment termination (for OCD, once phobic symptoms and compulsive beliefs are eliminated). Since, by its own nature, BST is aimed at solving complex problems in a short time, OCD symptoms release may be obtained even within the first encounters. This aspect should not be underestimated. In fact, even though the efficacy of CBT in treating OCD symptoms has been proven in several investigations,[41–43] it is different to be free from a debilitating disease in 2/3 months instead of 2/3 years. The efficiency of a treatment underlines the real therapeutic efficacy.

The BST research-intervention approach has been shown to be a valid method for acquiring operative knowledge on OCD. However, no empirical study has been conducted as yet. For this reason, an observational study aimed at empirically assessing the effect of the OCD-specific BST has been planned. Since it represents the first investigation that will statistically test the effects of the BST protocol for OCD, future controlled trials are required in order to better evaluate both the efficacy and the effectiveness of either BST alone or in combination with other treatment strategies in treating obsessive and compulsive symptoms.

Competing interests None declared.

REFERENCES

1. Keeley M, Storch EA. The nature, assessment, and treatment of pediatric obsessive-compulsive disorder. *Behav Psychol* 2008;16:535–51.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. Washington: American Psychiatric Press, 1994.
3. Karno M, Golding JM, Sorenson SB, *et al*. The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry* 1988;45:1094–9.
4. Abramowitz JS, Taylor S, McKay D. Obsessive-compulsive disorder. *Lancet* 2009;374:491–9.
5. Foa EB. Cognitive behavioral therapy of obsessive-compulsive disorder. *Dialogues Clin Neurosci* 2010;12:199–207.
6. Geffken GR, Storch EA, Gelfand KM, *et al*. Cognitive-behavioral therapy for obsessive-compulsive disorder: review of treatment techniques. *J Psychosoc Nurs Ment Health Serv* 2004;42: 44–51.
7. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* 1997;349:1436–42.
8. Torres AR, Fontenelle LF, Ferrão YA, *et al*. Clinical features of obsessive-compulsive disorder with hoarding symptoms: a multicenter study. *J Psychiatr Res* 2012;46:724–32.
9. Doron G, Moulding R, Kyrios M, *et al*. Sensitivity of self-beliefs in obsessive compulsive disorder. *Depress Anxiety* 2008;25: 874–84.
10. Keeley ML, Storch EA, Merlo LJ, *et al*. Clinical predictors of response to cognitive-behavioral therapy for obsessive-compulsive disorder. *Clin Psychol Rev* 2008;28:118–30.
11. Nardone G, Portelli C. *Ossessioni compulsioni manie. Capirle e sconfiggerele in tempi brevi*. Milano: Ponte delle Grazie, 2013.
12. Storch EA, Abramowitz J, Goodman WK. Where does obsessive-compulsive disorder belong in DSM-V? *Depress Anxiety* 2008;25:336–47.
13. Abramowitz JS. Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: a quantitative review. *J Consult Clin Psychol* 1997;65:44–52.
14. [No authors listed]. Treatment of obsessive-compulsive disorder. Expert Consensus Panel for Obsessive-Compulsive Disorder. *J Clin Psychiatry* 1997;58(Suppl 4):2–72.
15. van Oppen P, de Haan E, van Balkom AJ, *et al*. Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. *Behav Res Ther* 1995;33:379–90.
16. Abramowitz JS. The psychological treatment of obsessive-compulsive disorder. *Can J Psychiatry* 2006;51:407–16.
17. Doron G, Kyrios M. Obsessive compulsive disorder: a review of possible specific internal representations within a broader cognitive theory. *Clin Psychol Rev* 2005;25:415–32.
18. Meyer V. Modification of expectations in cases with obsessional rituals. *Behav Res Ther* 1966;4:273–80.
19. Lewin AB, De Nadai AS, Park J, *et al*. Refining clinical judgment of treatment outcome in obsessive-compulsive disorder. *Psychiatry Res* 2011;185:394–401.
20. Geller DA, Biederman J, Stewart SE, *et al*. Impact of comorbidity on treatment response to paroxetine in pediatric obsessive-compulsive disorder: is the use of exclusion criteria empirically supported in randomized clinical trials? *J Child Adolesc Psychopharmacol* 2003;13(Suppl 1):S19–29.
21. Storch EA, Björgvinsson T, Riemann B, *et al*. Factors associated with poor response in cognitive-behavioral therapy for pediatric obsessive-compulsive disorder. *Bull Menninger Clin* 2010;74:167–85.
22. Essays UK. Treatment of Obsessive Compulsive Disorder Psychology Essay. 2013. http://www.ukessays.com/essays/psychology/treatment-of-obsessive-compulsive-disorder-psychology-essay.php?cref=1
23. Nardone G, Portelli C. *Knowing through changing: the evolution of brief strategic therapy*. Glasgow: Crown House Publishing, 2005.
24. Nardone G, Balbi E. *Solcare il mare all'insaputa del cielo. Lezioni sul cambiamento terapeutico e le logiche non ordinarie*. Milano: Ponte alle Grazie, 2008.
25. Nardone G, Verbitz T, Milanese R. *The prisons of food: strategic solution-oriented research and treatment of eating disorders*. London: Karnac Publishing, 1999.
26. Nardone G, Watzlawick P. *Brief strategic therapy: philosophy, technique and research*. Lanham, MD: Jason Aronson, 2005.
27. Portelli C. Advanced brief strategic therapy for obsessive-compulsive disorders. *Brief Strateg Syst Ther Eur Rev* 2004;1:88–97.
28. Portelli C. Brief strategic interventions for obsessive compulsive disorders: acquiring the maximum with the minimum in the first session. *Brief Strat Syst Ther Eur Rev* 2005;2:56–70.
29. Austin JL. *How to do things with words*. Cambridge: Harvard University Press, 1962.
30. Nardone G, Watzlawick P. L'arte del Cambiamento: la soluzione dei problemi psicologici e interpersonali in tempi brevi. Milano: Ponte alle Grazie, 1990.
31. Embi PJ, Kaufman SE, Payne PR. Biomedical informatics and outcomes research: enabling knowledge-driven health care. *Circulation* 2009;120:2393–9.
32. Woody SR, Steketee G, Chambless DL. Reliability and validity of the Yale-Brown Obsessive-Compulsive Scale. *Behav Res Ther* 1995;33:597–605.
33. Kim SW, Dysken MW, Kuskowski M. The Yale-Brown Obsessive-Compulsive Scale: a reliability and validity study. *Psychiatry Res* 1990;34:99–106.
34. Tek C, Ulug B, Rezaki BG, *et al*. Yale-Brown Obsessive Compulsive Scale and US National Institute of Mental Health Global Obsessive Compulsive Scale in Turkish: reliability and validity. *Acta Psychiatr Scand* 1995;91:410–13.

35. Seol SH, Kwon JS, Shin MS. Korean self-report version of the Yale-Brown Obsessive-Compulsive Scale: factor structure, reliability, and validity. *Psychiatry Investig* 2013;10:17–25.
36. Wang YP, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Rev Bras Psiquiatr* 2013;35:416–31.
37. Beck AT, Ward CH, Mendelson M, *et al*. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–71.
38. Jacobson NS, Truax P. Clinical significance: a statistical approach to denning meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991;59:12–19.
39. Jacobson NS, Roberts LJ, Berns SB, *et al*. Methods for defining and determining the clinical significance of treatment effects: description, application, and alternatives. *J Consult Clin Psychol* 1999;67:300–7.
40. Manzoni GM, Cribbie RA, Villa V, *et al*. Psychological well-being in obese inpatients with ischemic heart disease at entry and at discharge from a four-week cardiac rehabilitation program. *Front Psychol* 2010;1:38.
41. Murray K, Jassi A, Mataix-Cols D, *et al*. Outcomes of cognitive behaviour therapy for obsessive-compulsive disorder in young people with and without autism spectrum disorders: a case controlled study. *Psychiatry Res* 2015;228:8–13.
42. Aslam M, Irfan M, Naeem F. Brief culturally adapted cognitive behaviour therapy for obsessive compulsive disorder: a pilot study. *Pak J Med Sci* 2015;31:874–9.
43. Oldfield VB, Salkovskis PM, Taylor T. Time-intensive cognitive behaviour therapy for obsessive-compulsive disorder: a case series and matched comparison group. *Br J Clin Psychol* 2011;50:7–18.