Differential effects of sertraline and cognitive behavioural therapy on behavioural inhibition in patients with obsessive compulsive disorder

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Patients with obsessive compulsive disorder (OCD) randomised to sertraline, manualised cognitive behavioural therapy (CBT), or combination (sertraline + CBT), underwent cognitive assessment. Cognitive testing was conducted at baseline and at week 16. The stop signal reaction time task (SSRT) was used to evaluate motor impulsivity and attentional flexibility was evaluated using the intra/extra-dimensional set shifting task. Paired-samples *t*-tests or nonparametric variants were used to compare baseline and posttreatment scores within each treatment group. Forty-five patients were tested at baseline (sertraline $n = 14$; CBT $n = 14$; sertraline + CBT $n = 17$) and 23 patients at week 16 (sertraline $n = 6$; CBT $n = 7$; sertraline + CBT $n = 10$). The mean dosage of sertraline was numerically higher in those taking sertraline as a monotherapy (166.67 mg) compared with those taking sertraline in combination with CBT (100 mg). Analysis of pre-post treatment scores using an intent-to-treat-analysis found a significant reduction in the SSRT in those treated with sertraline, whilst there was no significant change on this task for those treated with CBT or the combination. This study found that motor inhibition improved significantly following sertraline monotherapy. Suboptimal sertraline dosing might explain the failure to detect an effect on motor inhibition in the group receiving combination of sertraline + CBT. Higher dose sertraline may have broader cognitive effects than CBT for OCD, motor impulsivity may have value as a measure of treatment outcome and, by extension, the SSRT could serve as a biomarker for personalising care. *Int Clin Psychopharmacol* XXX: XXXX–XXXX Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Obsessive compulsive disorder (OCD) is a common and debilitating chronic mental health condition, associated with significant impairments in functioning and quality of life (Kochar *et al*., 2023), with a 12-month prevalence of approximately 1.2% (5th ed.; Diagnostic and Statistical Manual of Mental Disorders (DSM-5); American Psychiatric Association, 2013). From a neuropsychological perspective, problems with behavioural inhibition are fundamental mechanisms driving risk for OCD (Fineberg *et al*., 2010, 2018a; Chamberlain *et al*., 2018). According to meta-analysis, the aspects of behavioural inhibition that seem to be most reliably affected in OCD include prepotent motor inhibition and cognitive flexibility (specifically attentional flexibility) (Chamberlain *et al*., 2021; Clarke *et al*., 2023 *in submission*). These cognitive domains can be reliably measured using computerised tasks including, respectively, the stop signal reaction time task (SSRT) (Logan *et al*., 1984) and the intra/extra dimensional set shifting task (ID-ED) (Sahakian *et al*.,1992).

Standard treatment for OCD includes pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI) or psychological therapy with cognitive behavioural therapy (CBT) involving exposure and response prevention

(ERP), a behavioural technique whereby patients are exposed to and taught to tolerate conditions that provoke obsessions and compulsions and resist acting on them (National Institute of Health and Care Excellence, NICE, 2006). However, there is limited evidence to indicate which is more efficacious and the conditions in which one should be recommended over the other, or indeed, whether combination treatment (i.e. SSRI plus CBT) is more effective than monotherapy (Baldwin *et al*., 2014).

Fineberg *et al*. (2018b) conducted a feasibility study (optimal treatment for OCD; OTO study), which directly compared the effects of the SSRI sertraline as monotherapy, CBT as monotherapy, and combination treatment (sertraline and CBT) in a cohort of 49 adult patients with OCD. All three treatment arms demonstrated an improvement in OCD symptoms on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, Goodman *et al*., 1989), with no statistically significant between-group differences. At the primary endpoint (16 weeks from baseline), combination therapy was numerically superior in comparison to CBT, with a more modest advantage for sertraline compared to CBT. However, by weeks 32 and 52, there was a sustained numerical advantage for sertraline monotherapy when compared to both CBT monotherapy and combination treatment (Fineberg *et al*., 2018b). It was noted that the mean daily sertraline dosages were numerically higher in those taking sertraline as a monotherapy (166.67 mg) compared with those taking sertraline in combination with CBT (100 mg), which may have explained the added benefit seen for sertraline monotherapy.

Whilst the primary aim of the OTO study was to determine relative efficacy in terms of OCD symptomatology, additional aims included evaluating the differential effects of different forms of treatment on aspects of cognition known to be associated with OCD, that is, aspects of behavioural inhibition including motor impulse control and cognitive (attentional) flexibility, as core domains of executive dysfunction not readily captured by existing clinical rating scales such as the Y-BOCS (Fineberg *et al*., 2018a; Clarke *et al*., 2023 *in submission*).

Many studies have demonstrated that motor impulse control, for example, as measured by performance on the SSRT, a task based on the work of Logan *et al*. (1984), is impaired in individuals with OCD compared to healthy controls (Menzies et al, 2007; Lipszyc and Schachar, 2010; Boisseau *et al*., 2012; de Wit *et al*., 2012). To date, studies have generally demonstrated no significant association between performance on the SSRT and OCD symptom severity (Chamberlain *et al*., 2007a; McLaughlin *et al*., 2016; Clarke *et al*., 2023), suggesting motor impulsivity may represent a trait marker of OCD. One case-control study (Kalanthroff *et al*., 2017) directly compared SSRT performance in people with OCD who were or were not medicated and identified no significant difference between groups, providing further support for motor impulsivity as an enduring trait, which may not change with treatment or as the severity of the illness changes.

Other studies have linked attentional forms of inflexibility with OCD. A recent meta-analysis (Chamberlain *et al*., 2021) analysed pooled data from 11 studies employing the ID-ED in which patients with OCD were directly compared with healthy controls. Those with OCD committed significantly more errors on the extradimensional shift (EDS) element of the task, measuring attentional set shifting, than controls, with a moderate-large effect size (SMD = 0.62, P = 0.0004, 95% CI [0.28, 0.95]). These differences were not accounted for by age or intelligence quotient. A more recent, unpublished meta-analysis by Clarke *et al*. (2023 *in submission*) indicates that the magnitude of cognitive inflexibility broadly defined, including results of the ID-ED and versions of the Wisconsin Card Sort Test, is not altered by the severity of OCD symptomatology. These findings suggest that inflexible thinking (i.e. attentional inflexibility) may also represent a trait marker of OCD. In a series of older studies, unaffected relatives of patients with OCD were shown to have impaired SSRT and EDS performance of similar (possibly greater) magnitude compared to the affected probands (Chamberlain *et al*., 2007a; Menzies *et al*., 2007). Taken together with the evidence listed above, this suggests that motor inhibition and attentional flexibility may constitute cognitive trait markers for OCD, reflecting inherent aspects of motor impulsivity and compulsivity, respectively. They may additionally, however, reflect the presence of comorbidities commonly seen in OCD, such as trichotillomania, which is known to be associated with a prolonged SSRT (Chamberlain *et al*., 2006; Chamberlain *et al*., 2007b), and obsessive-compulsive personality disorder, which is associated with attentional inflexibility on the ID-ED task (Fineberg *et al*., 2015).

Aims and objectives

The aim of this secondary analysis of the OTO study (Fineberg *et al*., 2018b) is to directly explore relationships between key aspects of cognitive functioning germane to OCD (motor inhibition, attentional flexibility) and treatment response. The objectives were to investigate whether, using standardised tests of behavioural inhibition, that is, the SSRT and the ID-ED test, we could differentiate the treatment outcomes of the three major treatment strategies for OCD, that is, SSRI monotherapy, CBT with ERP, and combination treatment. We believe this to be the first study in patients with OCD to apply these tests of behavioural inhibition across these three different treatment arms within the same randomised controlled trial.

Methods

This is a secondary analysis of a previously published study (Fineberg *et al*., 2018b). In the following section we summarise key aspects of the methodology to aid

interpretation of our findings. Full methodological details are available in the original publication.

The study took place at three centres in the UK: Hertfordshire Partnership University NHS Foundation Trust, South West London and St. George's Mental Health NHS Trust, and Southern Health NHS Foundation Trust. Ethics approval for the trial was granted by the East of England NHS Ethics Committee, REC reference 13/EE/0431 (Approved 27/01/2014). All participants gave written informed consent, and trial conduct adhered to Good Clinical Practice (National Institute for Health Research).

Design

This was a three-arm, multi-centre, randomised feasibility study. The treatment arms were sertraline (flexibly titrated to 200 mg/day), CBT monotherapy, and combination therapy (sertraline flexibly titrated to 200 mg/day and CBT). Study participants were male or female community-based adults (aged 18–65 years) seeking treatment for OCD (which had to be at least moderate in severity) with a duration of symptoms of at least 1 year. Outcome assessments were performed by independent researchers blinded to treatment outcome, to reduce bias. The primary endpoint was 16 weeks with a final endpoint of 52 weeks.

The outcomes of interest for the current analysis are performance on two computerised neurocognitive tests, the SSRT and the ID-ED task, from the Cambridge Neuropsychological Test Automated Battery (Fray *et al.*, 1996) and specifically selected for their ability to reliably measure motor impulsivity and attentional flexibility. Tests were administered at baseline, weeks 16 and 52 by a blinded member of the research team who had received appropriate training. Study participants were encouraged to complete all assessments. Administration of the cognitive tests lasted approximately 60 min and participants were able to take short rest breaks between tests if needed.

Stop signal reaction time task

The SSRT tests motor response inhibition and impulse control. In this task, the participant is asked to respond to a 'go' stimulus presented as an arrow on a computer screen, by selecting one of two optional button-presses on the keypad, depending on the direction in which the arrow points. The subject is instructed that if they hear an audio tone presented alongside the arrow, they should withhold making that button-press response (prepotent inhibition). The SSRT is the key metric used for analysing this task. It is calculated from the response timings and refers to the time taken to inhibit the response provoked by the 'go' signal in the presence of the withhold signal. Increase in the length of the SSRT represents impairment in motor inhibitory control.

Intra-extra dimensional set shift

Cognitive flexibility is the mental ability to shift between thinking about two different concepts or to be able to think about multiple concepts simultaneously. The ID-ED is a computerised task, adapted from the Wisconsin Card Sorting Task (Berg, 1948), which follows a series of stages testing various aspects of flexible thinking, including rule acquisition and reversal as well as shifting and flexibility of attention.

During the test, participants are required to learn a rule about which one of two presented stimuli is correct through feedback given. After the participant has learnt the rule (evidenced by six consecutive correct responses), the rule changes and the participant must adapt their responses accordingly. There are nine stages to the task, assessing different components of rule acquisition, reversal and flexibility. Our analysis of performance on the ID-ED test examines two of the most pertinent outcome measures for attentional flexibility: 'total stages completed' (greater score = more flexible) and 'total errors adjusted' (greater score = less flexible).

Statistical analysis of neurocognitive data

JASP, free statistical software developed by the University of Amsterdam, was used for the statistical analysis of the cognitive data [JASP Team (2024). JASP (Version 0.16.3) (Computer software)]. Analysis of variance was used to detect differences in cognitive test performance between arms and paired samples Student's *t*-test to look at differences within arms by comparing baseline scores on the cognitive tests to the scores on the repeated tests at week 16 (pre-post effect sizes). Assumption checks were conducted using tests of normality (Shapiro–Wilk) and, when deviations from normality were present, non-parametric tests were used (Wilcoxon signed-rank test). For the Student's *t*-test, the effect size was calculated as Cohen's *d* (*d*), whilst for the Wilcoxon test, the effect size was calculated as the matched rank biserial correlation (r_{bs}). Correlation analyses were conducted to investigate possible associations between baseline cognitive scores and baseline Y-BOCS scores and multivariate regression analyses were run to explore possible predictive value of baseline cognitive scores or pre-post changes in cognitive scores for Y-BOCS scores at week 16 (outcome). A completer analysis and a last observation carried forward (LOCF) group analysis was carried out as this was a small feasibility study and because dropout rates at week 16 were relatively high and may potentially have confounded the findings based on completers alone. Linear and logistic regression models were used to investigate possible predictive factors of treatment response.

Results

Out of 49 patients randomised, 44 patients commenced treatment, of whom 35 (79.6%) completed 8 weeks in the study with 29 (65.9%) reaching the primary

endpoint (16 weeks). At the final endpoint (52 weeks) there were 23 (52.3%) participants remaining in the study. No significant differences were found between treatment arms in terms of participant dropout at either endpoint.

Baseline analysis

The three treatment groups were similarly matched at baseline although across the arms there were slightly more females. There was a mean total Y-BOCS score of 26.7 at baseline (for details of sample characteristics, see Fineberg *et al.*, 2018b).

We obtained full cognitive test data for 45 study participants at baseline (sertraline monotherapy $n = 14$, CBT monotherapy $n = 14$, combination arm $n = 17$), and for 23 of these we had additional scores at week 16 (6 participants in the sertraline monotherapy arm, 7 in the CBT monotherapy arm and 10 in the combination treatment arm).

In the baseline dataset, we found a significant moderate correlation between baseline Y-BOCS and baseline SSRT in the total sample (Pearson's $r = 0.428$, P-value = 0.003), whilst no significant correlation was found between baseline Y-BOCS and summary measures of ID-ED (total stages completed and total errors adjusted). We did not find any significant results on the multivariate regression analyses with baseline cognitive scores or pre-post changes in cognitive scores as predictors and Y-BOCS scores at week 16 as outcomes.

It was not possible to carry out an analysis using the data from the final end-point of the study (52 weeks) due to the sample size being too small (sertraline monotherapy $n = 5$, CBT monotherapy $n = 6$, combination treatment $n = 6$).

Stop signal reaction time

Completer analysis

Analysis of the completer group showed that those in the sertraline monotherapy arm demonstrated an improvement from baseline to week 16 on the SSRT with an effect size (paired samples t-test) of $d = 1.363$ (95% CI = 0.19–2.48) ($P = 0.021$). No significant within-group improvements were observed for the CBT monotherapy or combination treatment groups, with negative effect sizes of $d = -0.37$ (95% CI = −1.18 to 0.48) ($P = 0.411$) for the CBT monotherapy group and $d = 0.10$ (95% CI = −0.52 to 0.72) ($P = 0.754$) for the combination group (see Table 1 and Fig. 1).

Last observation carried forward

The LOCF analysis also demonstrated a significant improvement in SSRT under sertraline monotherapy (Wilcoxon signed-rank test) ($r_{bs} = 1.00$, $P = 0.036$). Similarly, in this analysis, no significant within-group improvements in the SSRT were seen for the combination treatment group ($r_{bs} = 0.07$, $P = 0.906$) or for the CBT monotherapy group ($r_{bs} = -0.29$, $P = 0.554$) (see Table 2 and Fig. 2).

Table 1 SSRT and ID-ED scores at baseline and Week 16 across CBT, sertraline and sertraline + CBT arms (completer analysis)

Group	Task (*N*)	Mean score at baseline (SD)	Mean score at week 16 (SD)
CBT	SSRT ($N = 6$)	207.36 (76.68) ms	222.37 (69.84) ms
	ID/ED total stages completed ($N = 6$)	8 (1.10)	7.33 (0.82)
	ID/ED total errors adjusted ($N = 7$)	44.43 (36.67)	51 (25.90)
SSRI	SSRT ($N = 6$)	**244.99 (60.83) ms**	**164.72 (24.38)*** ms
	ID/ED total stages completed ($N = 6$)	9 (0)	9 (0)
	ID/ED total errors adjusted ($N = 6$)	14 (7.46)	16.17 (5.95)
CBT + SSRI	SSRT ($N = 10$)	204.26 (74.73)	196.36 (64.77)
	ID/ED total stages completed ($N = 10$)	8 (1.05)	7.80 (2.53)
	ID/ED total errors adjusted ($N = 10$)	39.40 (20.48)	29.30 (19.58)

CBT, cognitive behavioural therapy; ID-ED, intra/extra dimensional set shift task; SSRI, selective serotonin reuptake inhibitor; SSRT, stop signal reaction time.
* $P < 0.05$, within-group change in score from baseline to week 16.

Intra/extra dimensional set shifting test

Analysis of the ID-ED test examined the 'total stages completed' and 'total errors adjusted'.

Completer analysis

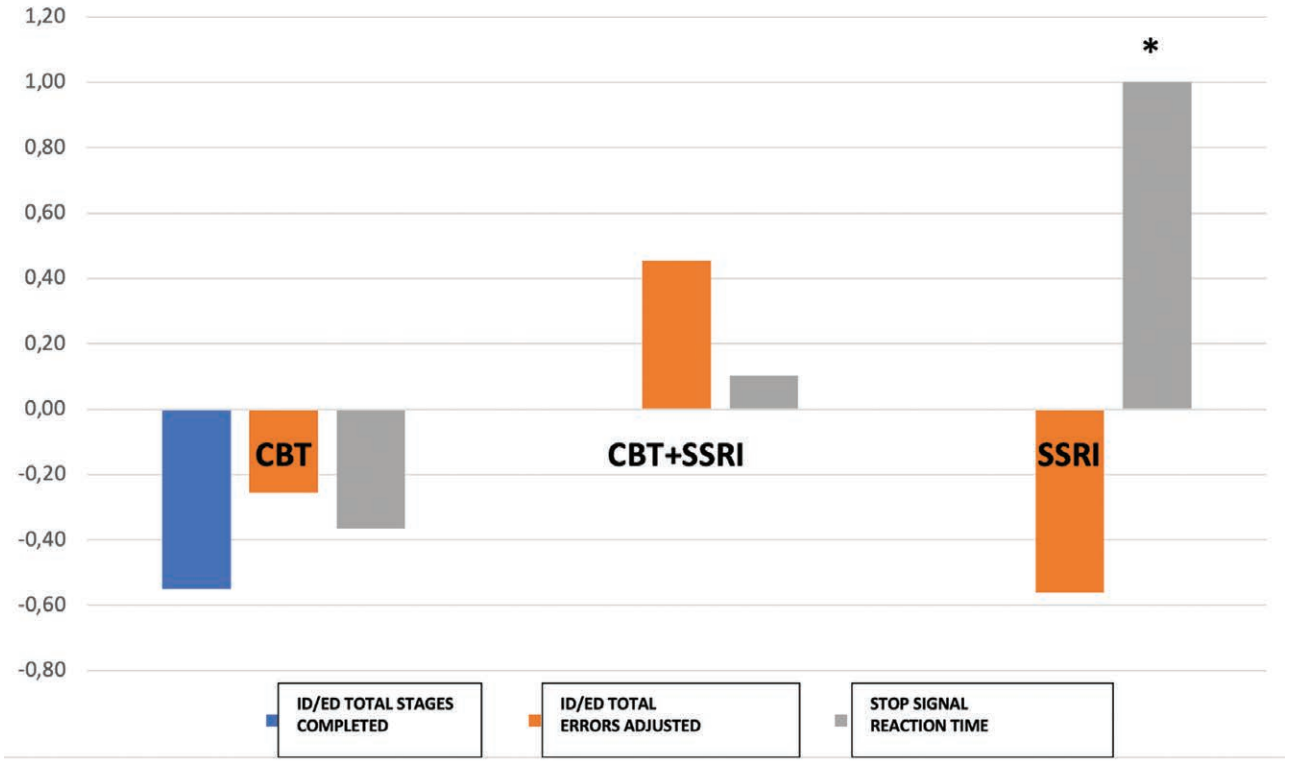
Looking at total stages completed on the ID-ED, those treated in the CBT monotherapy group showed an effect size (Wilcoxon signed-rank test) of $r_{bs} = 1.00$, but there was considerable heterogeneity and the result was not statistically significant ($P = 0.346$), whereas in the combination group the effect size was $r_{bs} = 0.00$ ($P = 1.00$). No effect size was possible to calculate for the sertraline monotherapy group as the variance in the difference of stages completed at baseline and at week 16 was equal to 0.

For total errors adjusted on the ID-ED, CBT monotherapy showed an effect size (paired sample t-test) of $d = 0.25$ (95% CI = −1 to 0.51) ($P = 0.526$), combination therapy an effect size of $d = 0.45$ (95% CI = 0.21–1.10) ($P = 0.185$) and sertraline monotherapy an effect size of $d = -0.56$ (95% CI = −1.41 to 0.33) ($P = 0.228$) (see Table 1 and Fig. 1).

Last observation carried forward

Looking at total stages completed on the ID-ED, in the LOCF analysis, the CBT effect size (Wilcoxon signed-rank test) was $r_{bs} = 1.00$ ($P = 0.346$). For the combination group the effect size was $r_{bs} = 0.00$ ($P = 1.00$). As above, it was not possible to calculate an effect size for sertraline due the variance in results being equal to 0.

Fig. 1



Effect size of SSRT and ID-ED total stages completed and total errors adjusted at baseline and 16 weeks across CBT, sertraline and sertraline + CBT arms – completers analysis. Effect sizes for the three groups (CBT, CBT + SSRI and SSRI) – corrected for non-normality when needed. In blue: ID/ED total stages completed; in orange: ID/ED total errors adjusted; in grey: stop signal reaction time (SSRT). Improvement: positive effect size. Worsening: negative effect size. *$P < 0.05$, within-group change in score from baseline to week 16. No column visible for ID-ED stages completed in the sertraline and sertraline + CBT arms because effect size = 0. CBT, cognitive behavioural therapy; ID-ED, intra/extra dimensional set shift task; SSRI, selective serotonin reuptake inhibitor.

For total errors adjusted on the ID-ED, the CBT monotherapy arm produced an effect size (Wilcoxon signed-rank test) of $r_{bs} = -0.29$ ($P = 0.554$), whilst the combination arm effect size was $r_{bs} = 0.49$ ($P = 0.213$) and for sertraline monotherapy the effect size was $r_{bs} = -0.800$ ($P = 0.197$) (see Table 2 and Fig. 2).

Discussion

The principal finding from our analysis was an improvement in motor impulsivity from baseline to 16 weeks endpoint (as measured by the SSRT) demonstrated selectively within the sertraline monotherapy arm. By contrast, the findings for the ID-ED task indicate that cognitive flexibility was not significantly altered in any of the treatment arms. It should be noted that the analyses involved relatively small sample sizes and high dropout rates, linked to the naturalistic nature of the participant group (Fineberg *et al.*, 2018b). Thus, we were unable to detect any between-arm differences and the dataset at the final endpoint was just too small for analysis. Moreover, we were unable to determine if these cognitive changes related to comorbid states, as there were just too few patients with relevant comorbidities for analysis. Nevertheless, our finding implies that there may be scope for improving motor impulsivity in patients with OCD who are treated with SSRIs. It is important to note that the combination treatment group were also exposed to sertraline [although taking it at a lower mean dose (100 mg daily) for reasons unrelated to study design – see Fineberg *et al.*, 2018b] but did not manifest the same SSRT improvement. This suggests that it may be only at the higher end of the SSRI-dosage range whereby improvements in motor impulsivity are possible.

As participants in the sertraline monotherapy group were the only group with an evidenced improvement in their SSRT scores, it appears unlikely that the improvement demonstrated in our results is a nonspecific learning effect of repeating the tests. Furthermore, performance on the ID-ED task seemed to worsen numerically (if not statistically) over time and in the sertraline arm, changes in the ID-ED task did not correlate with SSRT improvement, suggesting that motor impulsivity and cognitive inflexibility represent separable cognitive deficits within OCD, with only the former amenable to treatment-related improvement using SSRI or CBT.

Table 2 SSRT and ID-ED scores at baseline and week 16 across CBT, sertraline and sertraline + CBT arms (last observation carried forward)

Group	Task (*N*)	Mean score at baseline (SD)	Mean score at week 16 (SD)
CBT	SSRT (*N* = 12)	249.95 (175.79) ms	257.45 (172.66) ms
	ID/ED total stages completed (*N* = 13)	7.92 (1.04)	7.62 (0.96)
	ID/ED total errors adjusted (*N* = 14)	44.57 (28.72)	47.86 (22.90)
SSRI	SSRT (*N* = 14)	**234.22 (52.16)**	**199.82 (49.27)***
	ID/ED total stages completed (*N* = 14)	7.71 (2.55)	7.71 (2.55)
	ID/ED total errors adjusted (*N* = 14)	43.21 (59.36)	44.14 (58.81)
CBT + SSRI	SSRT (*N* = 17)	201.12 (78.45) ms	196.47 (73.19) ms
	ID/ED total stages completed (*N* = 17)	8.18 (1.01)	8.06 (2.01)
	ID/ED total errors adjusted (*N* = 17)	36.47 (21.93)	30.53 (21.22)

CBT, cognitive behavioural therapy; ID-ED, intra/extra dimensional set shift task; SSRI, selective serotonin reuptake inhibitor; SSRT, stop signal reaction time.
* $P < 0.05$, within-group change in score from baseline to week 16.

Skandali *et al.* (2018) investigated the effects of acute administration of high dose SSRI (escitalopram) on performance on the ID-ED and SSRT tasks in healthy volunteers and found that escitalopram administration was associated with 'opposite functional effects': namely, impaired cognitive flexibility (greater number of errors on the extra-dimensional set shift section of the ID-ED) and simultaneous improvement in motor inhibition (determined by improved SSRT). The authors postulated that this could be due to differing effects of SSRI treatment in different relevant brain regions possibly related to the representation of receptors and transporter proteins that are utilised in the process of serotonin reuptake. Our study findings suggest that these observed acute effects of SSRI, in terms of improvement in SSRT, may persist as treatment continues, at least to 16 weeks.

Chamberlain *et al.* (2005) found that motor impulsivity was impaired in unaffected first-degree relatives of OCD patients and postulated that this could be a cognitive endophenotype for OCD. Interestingly, the unmedicated relatives performed numerically worse on the SSRT than did affected probands, many of whom were receiving medication with SSRI, suggesting that SSRI may offer some possible benefit for patients with OCD and impaired motor impulse control (albeit the patient-relative difference in the previous study was not statistically significant). The results of our study demonstrate that improvements were made in motor impulse control following treatment with high-dose sertraline, though we were unable to demonstrate a correlation with magnitude of Y-BOCS improvement. Therefore, motor impulsivity, as measured on the SSRT, could represent a biomarker of OCD that is potentially modifiable with SSRI treatment. We duly note that this finding contrasts with a recent meta-analysis of Clarke *et al.* (2023 in submission), where motor impulsivity appears unrelated to treatment status. The reason for this discrepancy is unclear although it is possible that variations in the study methodologies pooled in the meta-analysis play a role. Further, well powered randomised controlled studies with longer follow up would help to clarify this matter.

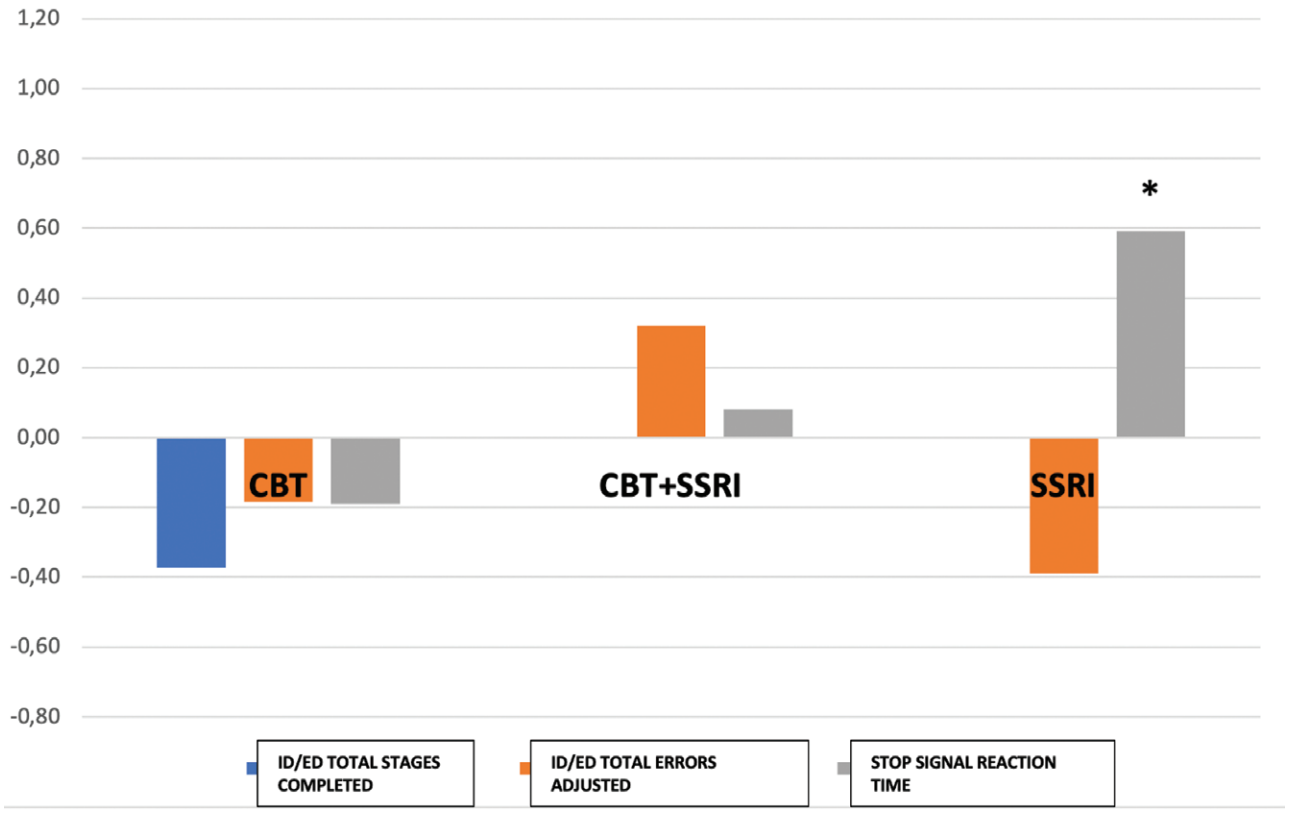
In contrast, the finding of no effect of sertraline on ID-ED performance is consistent with the findings of Vaghi *et al.* (2017) that ED shifting was not differentially affected in medicated and unmedicated patients with OCD, and also consistent with previous work on the effects of serotonin depletion on EDS performance in nonhuman primates (Clarke *et al.*, 2005). Chamberlain *et al.* (2005) reported that unaffected first-degree relatives of OCD patients show deficits in attentional set shifting on the ID-ED test, suggesting this aspect of cognitive inflexibility may represent another cognitive endophenotype. Gruner and Pittenger (2017) extended this hypothesis to suggest that cognitive inflexibility is a transdiagnostic trait marker, also occurring in patients with related disorders. However, other recent work has shown that medication can improve impairments in reversal learning in OCD (Sahakian *et al.*, 2023, in press), which is also consistent with the nonhuman primate evidence (Clarke *et al.*, 2005). One explanation may be that these different aspects of cognitive flexibility (attentional flexibility, reversal learning), which are both impaired in OCD, may reflect differences in neural circuitry and chemical neuromodulation.

Limitations

This was designed as a feasibility study. By testing three arms of treatment head-to-head, the number of participants in each cell was necessarily small. This limitation is exacerbated by the around 48% dropout rate (which is commonly seen in extended OCD clinical trials with naturalistic designs). Thus, we could not analyse data beyond 16 weeks, and even at that time point, numbers were too small for an adequate between-group analysis. Importantly, however, the finding of SSRT improvement in the sertraline arm was consistent across both the completer and the LOCF analyses, suggesting it is not simply a reflection of those with better impulse control preferentially remaining in the study.

With regards to missing data, we had a full neurocognitive data set (baseline and week 16 measures) for 52% of patients who initiated treatment. Missingness was largely due to study participants dropping out during the study (29 out of 56 remained in the study at 16 weeks). Our study protocol did not allow a separate visit for cognitive testing and thus it was incorporated into the clinical visits. Factors contributing to the noncompletion rates include the necessarily lengthy assessments on those rating days, as well as complexities relating to training in

Fig. 2



Effect size of SSRT and ID-ED total stages completed and total errors adjusted at baseline and 16 weeks across CBT, sertraline and sertraline + CBT arms – last observation carried forward analysis. Effect sizes for the three groups (CBT, CBT + SSRI and SSRI) – corrected for non-normality when needed. In blue: ID/ED total stages completed; in orange: ID/ED total errors adjusted; in grey: stop signal reaction time (SSRT). Improvement: positive effect size. Worsening: negative effect size. *$P < 0.05$, within-group change in score from baseline to week 16. No column visible for ID-ED total stages completed in the sertraline and sertraline + CBT arms because effect size = 0.

cognitive evaluations. Based on the results of this study, a study focusing on cognitive testing in OCD using tests delivered in a form designed to be engaging for a clinical population should be prioritised.

In sum, the findings of this study suggest that patients with OCD showed additional improvement in motor impulse control when treated with sertraline in optimised dosages but not CBT or sertraline (in lower dose) plus CBT. There is a clear need for larger studies to examine this area further. Moreover, if these findings were replicated in larger cohorts, this could have important clinical implications in terms of precision medicine and tailoring personalised care. For example, it may be possible for cognitive testing to be utilised routinely as part of the initial assessment to identify which of the available treatments might be more suitable for a patient, so personalising treatment plans.

Conclusion

In a study of patients with OCD limited by sample size, high dose sertraline treatment was associated with a beneficial effect on objective measures of motor inhibition, with implications for developing new precision-medicine approaches.

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Conflicts of interest

N.A.F. discloses the following: relationship with European Cooperation in Science and Technology, the University of Hertfordshire, the National Institute of Health Research, Orchard and UK Research and Innovation (UKRI) that includes: funding grants; relationship with Global Mental Health Academy and Children and Screens that includes: speaking and lecture fees; relationship with European College of Neuropsychopharmacology, British

Association for Psychopharmacology, World Psychiatric Association, Royal College of Psychiatrists and Italian Society of Biological Psychiatry that includes: travel reimbursement; relationship with Orchard and the European College of Neuropsychopharmacology that includes: board membership; relationship with Elsevier that includes: payment for editorial work. D.S.B. is a Medical Patron of Anxiety UK and President of the British Association for Psychopharmacology. During the course of the study, he was a Clinical Advisor to the National Clinical Audit of Anxiety and Depression and Chair of the Psychopharmacology Committee of the Royal College of Psychiatrists, his employer received research funding from NIHR and EU FP7, and he received personal fundings (lecture fees) from AstraZeneca and Janssen. T.W.R. has carried out consultancy work for Cambridge Cognition and Supernus. He also has received a research grant from Shionogi and editorial honoraria from Elsevier and Springer-Nature. S.R.C. receives honoraria from Elsevier for associate editor work at Comprehensive Psychiatry; and Neuroscience & Biobehavioral Reviews. For the remaining authors, there are no conflicts of interest.

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