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Concurrent oculomotor hyperactivity and deficient anti-saccade performance in obsessive-compulsive disorder

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ABSTRACT

Existing studies mainly focused on the inhibition of the task-interfering response to understand the inhibitory deficits of obsessive-compulsive disorder (OCD). However, recent studies suggested that inhibitory function is broadly involved in response preparation and implementation. It is yet unknown if the inhibition dysfunction in OCD extends beyond the task-interfering response to the general inhibitory function. Here we address this issue based on the multidimensional eye-movement measurements, which can better capture the inhibitory deficits than manual responses. Thirty-one OCD patients and 32 healthy controls (HCs) completed the anti-saccade task where multidimensional eye-movement features were developed. Confirmatory factor analysis (CFA) suggested two components of inhibitory function that negatively correlated with each other: one component of oculomotor hyperactivity in generating oculomotor output which is characterized with early premature saccades, early cross rates and saccade number; the other component of task-specific oculomotor efficiency which is characterized with task accuracy, saccade latency, correction rate, and amplitude gain. Importantly, OCD showed both stronger oculomotor hyperactivity and deficient oculomotor efficiency than HCs, and the machine-learning-based classifications showed that the features of oculomotor hyperactivity had higher prediction accuracy than the features of oculomotor efficiency in distinguishing OCD from HCs. Our results suggested that OCD has concurrent deficits in oculomotor hyperactivity and oculomotor efficiency, which may originate from a common inhibitory dysfunction.

1. Introduction

Obsessive-compulsive disorder (OCD) is a highly disabling mental disorder, with a lifetime prevalence of 2–3% (Stein et al., 2019), and leads to low life quality and high economic cost (Marazziti et al., 2002; Yang et al., 2021). The core characteristics of OCD are recurrent intrusive thoughts and repetitive undesired behaviors (Pauls et al., 2014). The cortico-striato-thalamo-cortical (CSTC) model proposed deficits in the frontal-striatal circuits as the pathophysiology of OCD (Menzies et al., 2008; Saxena and Rauch, 2000). A neuropsychological model suggested that the deficits in inhibitory function can be the endophenotypic markers of OCD, as the failures in behavioral inhibition bridge the frontal-striatal dysfunction and the symptoms (Chamberlain et al., 2005).

The inhibitory function can be probed by tasks such as Go/No-Go, Stop-signal and Anti-saccade where a prepotent motor response has to be stopped or overcome by a goal-directed response (Chambers et al., 2009). In Go/No-Go, a manual response has to be made quickly for a Go stimulus but has to be withheld for a No-Go stimulus (Logan, 1994). In Stop-signal, a manual response has to be made quickly after the target onset but has to be cancelled upon a sudden stop-signal (Verbruggen and Logan, 2008). In Anti-saccade, an eye movement has to be made to the

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target at a peripheral location in one context (prosaccade) but has to be directed to the opposite location in the other context (anti-saccade, Munoz and Everling, 2004). The impaired inhibition such as more commission errors in Go/No-Go, slower response cancellations in Stop-signal, and more anti-saccade errors, can be taken as the endophenotypic markers of OCD (Bari and Robbins, 2013; Chamberlain et al., 2005; Mar et al., 2022; Menzies et al., 2007).

While the function of inhibitory control can be captured by how well the task-interfering responses are overcome, it covers a broader scope as generally underlined response control, including but not restricted to response preparation, response selection and response inhibition (Duque et al., 2017). For instance, the motor-evoked potentials (MEPs) were consistently inhibited during response preparation (Greenhouse et al., 2015; Labruna et al., 2013), which was suggested to prevent the premature release of the response (Duque et al., 2010). The motor inhibition before the response output was also critically modulated by the competition between the alternative response options, suggesting the role of motor inhibition in response selection (Klein et al., 2014; Wang et al., 2019, 2021). Considering the general inhibitory function in motor/oculomotor control, together with the circuital connection between the thalamus and the brain areas for motor (e.g., supplementary motor area, SMA) and oculomotor (e.g., frontal eye fields) output (Alexander et al., 1986, 1990), the deficits of OCD would be broadly observed in the motor system. However, the dysfunction of response inhibition was often treated as covering a relatively narrower scope, that is, the dysfunctional inhibition of the task-interfering response. This view can be seen through the standard measurements in response inhibition tasks such as stop-signal reaction time (SSRT), No-Go errors, and anti-saccade accuracy. That is, the dysfunctional response inhibition was measured by how well the task-interfering response was withheld during the response implementation stage. Therefore, it is yet unknown if the inhibition dysfunction in OCD covers a broader scope to be generally involved in the preparation and implementation of response.

It has been shown that OCD exhibited hyperactivity in the motoric areas such as the premotor cortex and SMA (de Wit et al., 2012; Page et al., 2009). Therefore, the motor hyperactivity would lead to more response outputs or/and early response releases. However, such outputs may not be captured by conventional manual tasks, and this issue can be addressed by eye-movement measurements. First, in conventional tasks, the motor outputs were often parsimoniously obtained to render a univariate measurement such as SSRT or No-Go errors, which can be taken as the outcome of the inhibition. In an extension of the outcome measurement, eye-movement recording can render "process" measurements during the processes that entail response preparation and implementation. Second, the motor threshold for a manual response can be too high for the premature motor activity to be read out, whereas eye-movement measurements are more sensitive to capture the premature motor activity. Third, eye movements have the advantage of containing rich information at both the spatial and the temporal dimensions to achieve higher diagnostic power (Basel et al., 2023).

Here we adopted the anti-saccade task to show the oculomotor characteristics of OCD. We hypothesized that, relative to healthy controls (HCs), OCD would not only show lowered anti-saccade performances as reflections of impaired inhibition on task-interfering response, but also more or/and earlier oculomotor releases as reflections of the general motor hyperactivity. For our research purpose, we first identified multiple eye-movement features and tested their validity in representing the oculomotor activities related to task-general hyperactivity in the motor system and the oculomotor activities related to task-specific performance. We termed the former oculomotor hyperactivity (OH) and the latter oculomotor efficiency (OE). Then, we investigated how these eye-movement features differed between OCD and HCs. Next, we evaluated the effectiveness of these features in distinguishing OCD from HCs. Building on previous findings that motor inhibition during response preparation was more sensitive in predicting the inhibitory dysfunction (Quoilin et al., 2018, 2021), we expected that the OH features would be more effective in distinguishing OCD and HCs. Testing this hypothesis can also add to evaluating the capacities of these signatures as endophenotypic markers of OCD.

2. Materials and methods

2.1. Participants

Thirty-one OCD patients (15 females, 18–41 years old) and 32 HCs (15 females, 20–42 years old) participated the experiment (Table 1). OCDs were recruited from the outpatient clinic of Shanghai Mental Health Center. A structured interview was conducted by a licensed psychiatrist and trained graduate students. Specifically, patients were diagnosed by a licensed psychiatrist according to DSM-5 using the Mini International Neuropsychiatric Interview 7.0.2 (MINI) (Sheehan et al., 1998). In addition to MINI, psychopathological symptoms (OCD, depression, anxiety) were assessed with the Yale-Brown Obsessive--Compulsive Scale (Y-BOCS, Goodman et al., 1989), the Hamilton

Table 1
Demographic and clinical characteristics of OCD and HC.

	OCD	HC	Statistic[a]	*p*	*Cohen's d*
N	31	32			
Medication (Yes)[b]	22	0			
Age, years (SD)	27.77 (6.13)	26.16 (5.38)	$t(61) = 1.11$	0.27	
Gender, % male	51.61	46.88	$\chi^2(1) = 0.14$	0.71	
Dominant eye, % right	74.19	71.88	$\chi^2(1) = 0.04$	0.84	
Education, years (SD)	15.94 (1.75)	16.25 (1.34)	$t(61) = 0.80$	0.43	
Intelligence (SD)[c]	101.13 (8.98)	105.78 (7.75)	$t(60) = 2.19$	0.03	0.560
Y-BOCS (SD)[d]	20.81 (3.33)	0.56 (1.24)	$t(38.0) = 31.77$	<0.001	8.053
-Obsessions (SD)	10.06 (1.98)	0.34 (0.83)	$t(39.9) = 25.26$	<0.001	6.400
-Compulsions (SD)	10.74 (2.11)	0.22 (0.55)	$t(34.0) = 26.85$	<0.001	6.814
HAMD-17 (SD)	6.10 (3.57)	1.44 (1.37)	$t(38.4) = 6.80$	<0.001	1.723
STAI-S (SD)[e]	42.79 (13.81)	31.47 (6.77)	$t(44.2) = 4.23$	<0.001	1.070
STAI-T (SD)[e]	53.00 (11.60)	37.19 (6.66)	$t(61) = 6.85$	<0.001	1.727

OCD: obsessive-compulsive disorder, HC: healthy controls, SD: standard deviation, YBOCS: Yale-Brown obsessive-compulsive scale, HAMD-17: the 17-item Hamilton Depression Scale, STAI-S: the State-Trait Anxiety Inventory – State, STAI-T: the State-Trait Anxiety Inventory – Trait.

[a] Two-tailed independent *t* tests and Chi-square tests were performed for between-group comparisons.

[b] There were 22 medicated and 9 unmedicated patients (6 drug-naïve patients and 3 patients who had been withdrawn for at least 8 weeks).

[c] The intelligence score was measured by the Wechsler Intelligence Scale. The intelligence score of one OCD was not obtained due to the unwillingness to complete the inventory.

[d] Y-BOCS consists of obsessions and compulsions subscales.

[e] The STAI scores of two OCDs were not obtained due to their unwillingness to complete the inventory.

Depression Rating Scale (HAMD-17, Hamilton, 1960), and the State-Trait Anxiety Inventory (Spielberger, 1983) by well-trained clinical psychologists and graduate students. The inclusion criteria were: 1) 18–50 years old with at least middle-school education to ensure the capability of understanding and completing the task; 2) meeting the OCD criteria of DSM-5; 3) scoring ≥ 16 on the Y-BOCS; 4) unmedicated or having stopped medication for at least 8 weeks or having been stably medicated for at least 8 weeks. The exclusion criteria were: 1) DSM-5-defined mental disorder other than OCD covered by the MINI 7.0.2; 2) scoring ≥ 17 on the HAMD-17; 3) scoring <70 on Wechsler Intelligence Scale; 4) with symptoms of hoarding; 5) with clinically verified suicidal feelings; 6) with acute physical disease, central nervous disease, or substance dependence; 7) with current pregnancy or breastfeeding.

HCs were recruited from the general population and were examined by the structured interview. They were be firstly assessed using the MINI by well-trained clinical psychologists and graduate students to confirm no diagnosis of psychiatric disorders, and the rest process was the same as the one for patients. None of them had a history of mental disorders or had taken any psychoactive medication in the past 3 months. HCs were excluded if they had any family history of psychiatric disorders. All patients and HCs reported no chronic neurological diseases. Written informed consent was obtained before the experiment.

2.2. Apparatus and tools

Participants were tested individually in the laboratory of the outpatient clinics. Each participant was seated in front of a laptop screen (34.5 × 19.5 cm), with the head positioned on a chin-rest. The eye-to-screen distance was 75 cm. Eye movements were recorded from the dominant eye using Eyelink Portable Duo (SR Research, Canada, sampling rate 1000 Hz), a common apparatus in the field (Holmqvist et al., 2011). A standard procedure of five-point calibration and validation was performed at the experiment beginning.

2.3. Design and procedure

The design and procedure followed the general protocol of the anti-saccade paradigm (Munoz and Everling, 2004). A grey rectangle (13.1° × 7.4°) was presented at the screen center as the stimuli window throughout the experiment (Fig. 1a). Each trial started with a red or green central disc (1° diameter), lasting for 450/600/750/900ms. Participants were instructed to fixate on the central disc. The color (red vs. green) indicated whether the current trial was prosaccade or anti-saccade, and the mapping between the color and the trial type was counterbalanced across participants. Then, together with the central disc, a white disc (1° diameter) was presented for 500ms at the left or right border of the grey rectangle. Participants were required to look at the white disc with their eyes given a prosaccade trial, and to look at the opposite location given an anti-saccade trial. Participants were instructed to respond as accurately and quickly as possible. A blank screen of 1500 ms was presented after the target. There were 40 trials in each condition. The total 80 trials were mixed and divided into 4 blocks of equal length. Trials of the two conditions within each block were presented with equal probability and in a random order.

2.4. Identification of eye movements

For each trial, eye-movement data was obtained from the target onset to the offset of the blank screen. Eye blinks and saccadic events were detected based on the default algorithm of SR research. Saccadic events that contained eye blinks were excluded from analysis. Trials with initial saccade latency exceeding 600 ms relative to the target onset were discarded due to the lack of task engagement (Narayanaswamy

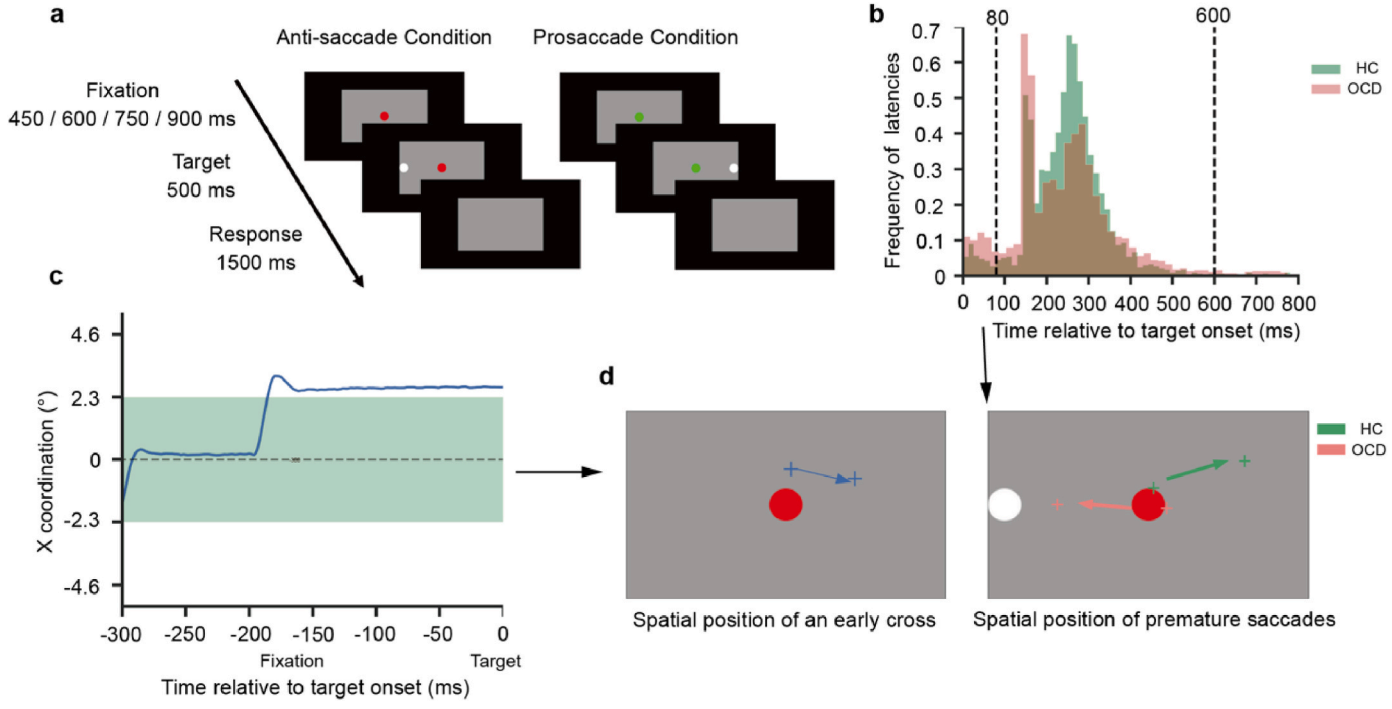

Fig. 1. (**a**) A trial sequence in the anti-saccade condition (left) and the prosaccade condition (right). (**b**) Frequency distribution of initial saccade latencies relative to the target onset. The two dashed lines in the graph represent saccade latencies of 80 ms and 600 ms. The initial saccades with latencies below 80 ms were identified as early premature saccades. (**c**) The data shown here are the gaze positions (*x* coordinates) as a function of time (relative to target onset) in an anti-saccade trial from one example participant. This case shows an early cross, which is defined as gazes that had moved away from the central fixation (<2.3° to the center, illustrated as green) before the target onset. (**d**) The spatial representations of early crosses (left) and premature saccades (right). The left panel shows an early saccade that had been initiated and deviated from the central fixation before the target onset. The right panel shows the trajectory of the initial saccades with latencies below 80 ms relative to the target onset. "+" indicates gaze positions, and arrows indicate the direction between consecutive gaze positions.

et al., 2021; van Zoest et al., 2004). For the remaining trials, we defined the following features.

Firstly we identified the initial saccades with latencies below 80 ms (Bey et al., 2018) (Fig. 1b). These saccades can reflect the inhibitory function, considering that a well-functioned motor inhibition underlines not only the successful inhibition of an incorrect motor response but also the prevention of premature motor release (Duque et al., 2010). They were termed early premature saccades.

While the early premature saccades captured the impaired inhibition in the time domain, next we identified the impaired inhibition in the spatial domain (Fig. 1c). Before the target onset, there were cases where the starting position of the initial saccade after the target was already away from the central fixation. Following Bey et al. (2018), the x coordinates of the gaze position deviated more than 2.3° from the central disc were taken as early crosses.

For trials that did not involve the early premature saccades and the early crosses, we calculated the number of saccades per trial to quantify the activity of the oculomotor system (Takahashi et al., 2021).

Then we identified the eye-movement features related to the task performance: accuracy, latency of the first saccade, correction rate and amplitude gain of the first saccade. In both the prosaccade and the anti-saccade condition, a correct response in a specific trial was identified if the first saccade after target onset was directed toward the correct direction (i.e., the target direction in the prosaccade condition and the opposite direction of the target in the anti-saccade condition) (Bey et al., 2018). For each condition, the accuracy was calculated as the proportion of correct trials. Corrections were identified in incorrect trials where the incorrect first saccade was followed by a saccade in the opposite direction with an amplitude exceeding 6.5° (half the width of stimuli window) (Bowling et al., 2012). Amplitude gain was calculated as the amplitude (in ° along the x-axis) of the first saccade divided by the target amplitude (in ° along the x-axis) (Rycroft et al., 2006). The target amplitude was defined as the distance between the target and the starting position of the first saccade such that the two amplitudes were calculated relative to the same reference point. The correctness of the saccade was considered in the calculation such that the amplitude was positive given a correct response and was negative given an incorrect response. A value of amplitude gain closer to 1 indicated higher proximity to the correct position whereas a value closer to −1 indicated higher proximity to the mirror position.

2.5. Statistical analysis and significance testing

The above features were calculated per condition, block and participant, and were assigned into two categories: one category reflected OH, including the early premature saccades, the early crosses, and the number of saccades; the other category reflected OE, including the accuracy, the latency of the first saccade, the correction rate and the amplitude gain of the first saccade. A confirmatory factor analysis (CFA) was conducted to test the validity of this dichotomy with 2-factor model. An alpha = 0.05 was set as the threshold for significance testing.

We then tested if the above features were distinct between the OCD group and HCs. The Levene's tests on the homogeneity of variance showed that early premature saccade, the number of saccades, and correction rate met the homogeneity assumption, all $p > 0.1$., whereas early crosses, $F(3, 122) = 4.30$, $p = 0.006$, accuracy, $F(3, 122) = 15.51$, $p < 0.001$, latency, $F(3, 122) = 5.27$, $p = 0.002$, and amplitude gain, $F(3, 122) = 9.94$, $p < 0.001$, did not meet the homogeneity assumption. For feature that met the homogeneity assumption, a 2 (group: OCD vs. HC) * 2 (condition: prosaccade vs. anti-saccade) mixed ANOVA was conducted, with the group included as a between-subject factor and condition included as a within-subject factor. For features that did not meet the homogeneity assumption, non-parametric analyses were taken as the alternative to evaluate both the main effects and the interaction (Ye et al., 2019). Specifically, Welch's t-test and Wilcoxon matched-pairs signed-rank test were used as the alternatives for independent and paired t tests, respectively (Zhang et al., 2019), to assess the group and the condition effect. The condition effects (anti-saccade vs. prosaccade) between groups were compared using Welch's t-test to assess if there was an interaction. Cohen's d was calculated as the effect size for both conventional t-test and Welch's t-test, and Rank-Biserial correlation coefficient was calculated as the effect size for Wilcoxon signed-rank test. An alpha = 0.05 was set as the threshold for significance testing, and a further t-test was performed following a significant interaction. The significance evaluation of the t tests was assessed based on two-tailed p-values because there were two directions of the difference. For the following classifications, we included the features that showed a significant difference between conditions or groups. In case there would be insignificant effects where the statistical power of the null effect was not clear, the Bayes Factor analysis was introduced to assess to which extent the null hypothesis is likely to be true (Wagenmakers et al., 2018). We also explored if the features that showed a significant interaction between condition and group could predict the compulsion scores by performing Pearson correlations. As no evidence to our knowledge has shown which specific eye movement features would show such a correlation, the specific features would be decided after the interaction. Given that the testing was nevertheless post-hoc rather than a priori, the significance was assessed based on one-tailed p values (Ludbrook, 2013). For a comprehensive view, the correlations between each feature and each clinical symptom are presented in Supplementary Table S1.

Next, we assessed the effectiveness of the eye-movement features in classifying the OCD group and HCs. We used a machine-learning algorithm to train and cross-validate classifiers based on the eye-movement features in discriminating the two groups of participants. This was implemented with the scilit-learn package (http://github.com/scikit-learn, Pedregosa et al., 2011). To show the predictability of the different categories of features, we performed the cross-validated classification separately on the features representing OH, the features representing OE, and the combined features of the two categories. For each round of testing, a 5-fold-leave-oue-out cross-validated classification was performed using a support vector machine classifier (SVM). This procedure was repeated 1000 times while ensuring that the assignment of the 5-fold samples was never repeated. Mean accuracies with 95% confidence intervals (CIs) were obtained to show the effect size. Permutation testing (n = 1000) was performed to show which category of features had higher predictability power. Statistical significance was assessed by calculating the probability of the unpermuted mean accuracy difference in the distribution of the permuted differences. An alpha = 0.05 was set as the threshold for significance testing, and multiple comparisons were Bonferroni-corrected.

3. Results

3.1. Demographical and clinical characteristics

As shown in Table 1, the two groups did not show significant differences in either age, gender, eye dominance or education. However, HCs showed higher intelligent higher scores than OCD. To control the potential confounding effects of intelligence on the eye movement results, we sorted the participants in each group into high-intelligence sub-group and low-intelligence sub-group based on the median score within each group. No significant differences between high- and low-intelligence were observed in either OCD or HCs (Supplementary Fig. S1). These results suggested that the current eye movement results were not due to the intelligence difference. Importantly, relative to HCs, OCD showed stronger obsession, compulsion and anxiety scores than HCs (Table 1).

3.2. CFA results

The 2-factor CFA model showed a good fit (Fig. 2), $\chi^2(3, N = 252) = 36.03$, $p < 0.05$, CFI = 0.968 (>0.9), GFI = 0.962 (>0.9), NNFI = 0.949

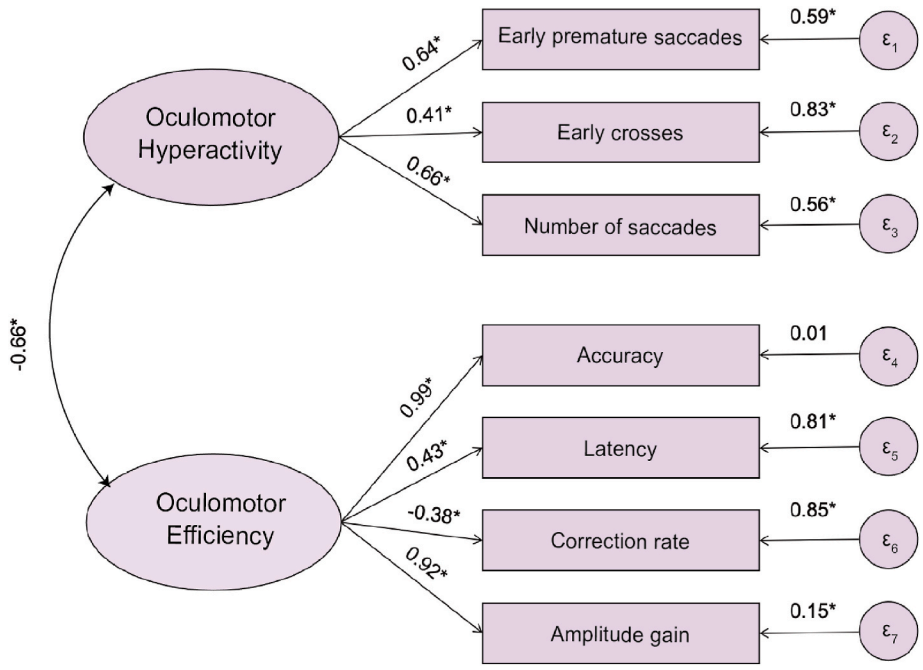

Fig. 2. Results of the 2-factor CFA model. ε denotes residual. *$p < 0.001$.

(>0.9), RMSEA = 0.084 (<0.1), SRMR = 0.056 (<0.1), TLI = 0.949 (>0.9), and $p < 0.001$ for all factor loadings. Significant factor loadings indicated that the variances of the assigned features were significantly accounted by the corresponding factors. Moreover, there was a strong negative correlation between the two factors, *Pearson* $r = -0.665$, $p < 0.001$.

3.3. Results of eye-movement features

The ANOVA on the rates of early premature saccades revealed a significant main effect of group, $F(1, 61) = 11.70$, $p = 0.001$, $\eta^2 = 0.124$, with OCD (8%) exhibiting higher rates of early premature saccade than HCs (4%, Fig. 3a). Neither the main effect of the experimental condition nor the interaction, both $F < 1$, reached significance. These results suggested impaired function of inhibiting early premature saccades in OCD.

The Welch's *t*-test on the early crosses showed a significant main effect of group, $t(86.47) = 5.06$, $p < 0.001$, Cohen's $d = 0.898$, with higher cross rate in OCD (16%) than HCs (5%, Table 2 and Fig. 3b). Neither the main effect of experimental condition nor the interaction between group and condition reached significance, both $p > 0.56$.

The ANOVA on the number of saccades showed a significant main effect of group, $F(1, 61) = 6.70$, $p = 0.012$, $\eta^2 = 0.094$, with more saccades in OCD (11.0 per trial) than HCs (8.1 per trial, Table 2 and Fig. 3c). There was also a main effect of condition, $F(1, 61) = 13.99$, $p < 0.001$, $\eta^2 = 0.010$, with more saccades in the anti-saccade condition (10.0) than in the prosaccade condition (9.1). However, the interaction was not significant, $F(1, 61) = 1.14$, $p = 0.29$.

The Welch's *t*-test on accuracy showed a main effect of group, $t(107.00) = 2.39$, $p = 0.018$, Cohen's $d = 0.428$, with lower accuracy in OCD (77%) than in HCs (86%). The Wilcoxon signed-rank test showed a main effect of condition, $z = 6.23$, $p < 0.001$, Rank-Biserial correlation coefficient = 0.918, with lower accuracy in the anti-saccade condition (69%) than in the prosaccade condition (94%, Table 2 and Fig. 3d). Moreover, there was an interaction between group and condition, $t(52.32) = 2.10$, $p = 0.041$, Cohen's $d = 0.531$. Further *t* tests showed that the group difference was significant only in the anti-saccade condition (15%), $t(55.672) = 2.67$, $p = 0.020$, Cohen's $d = 0.674$, but not in the prosaccade condition (3%), $t(44.30) = 1.68$, $p = 0.198$.

The Wilcoxon signed-rank test on the latency showed only a main effect of condition, $z = 6.05$, $p < 0.001$, Rank-Biserial correlation coefficient = 0.877, with significantly longer latency in the anti-saccade condition (266 ms) than in the prosaccade condition (237 ms, Table 2 and Fig. 3e). This result indicated the validity of the anti-saccade task in probing response inhibition. However, neither the main effect of group, nor the interaction reached significance, both $p > 0.3$.

The ANOVA on the correction rate did not show any significant effects, all $p > 0.11$ (Fig. 3f). We further performed the Bayes Factor (BF) analysis to assess the reliability of the non-significant effect. The results did not show strong evidence for a null effect, all BF values within the range of 0.3–1, as BF values higher than 3 or lower than 1/3 were suggested as acceptable (Wagenmakers et al., 2018). Given that the null hypothesis cannot be accepted, the correction rate was still included in the classification analysis.

The Welch's *t*-test on the amplitude gain showed a main effect of group, $t(111.22) = 3.30$, $p = 0.001$, Cohen's $d = 0.590$, suggesting that the landing precision was lower in OCD (55%) than HCs (76%, Table 2 and Fig. 3g). The main effect of condition was also significant, $z = 6.00$, $p < 0.001$, Rank-Biserial correlation coefficient = 0.870, with lower precision in the anti-saccade condition (47%) than in the prosaccade condition (84%). Moreover, there was also an interaction, $t(44.97) = 2.374$, $p = 0.022$, Cohen's $d = 0.601$. This interaction was due to that the lower precision in OCD relative to HCs was statistically more robust in the anti-saccade condition (mean difference 33%), $t(56.38) = 3.26$, $p = 0.004$, Cohen's $d = 0.822$, than in the prosaccade condition (mean difference 10%), $t(60.81) = 2.30$, $p = 0.050$, Cohen's $d = 0.579$.

In addition, both the accuracy and the amplitude gain in the anti-saccade condition showed a negative correlation with the compulsion scores of Y-BOCS among the OCD individuals, *Pearson* $r = -0.336$, $p = 0.032$ for accuracy (Fig. 3h), *Pearson* $r = -0.338$, $p = 0.031$ for amplitude gain (Fig. 3i). However, the correlations were not observed in the prosaccade condition, both $p > 0.1$. These results suggested that the accuracy and precision of anti-saccade can be used to predict the compulsive symptoms of OCD. The full correlation results between each feature and each clinical symptom are shown in Supplementary Table S1.

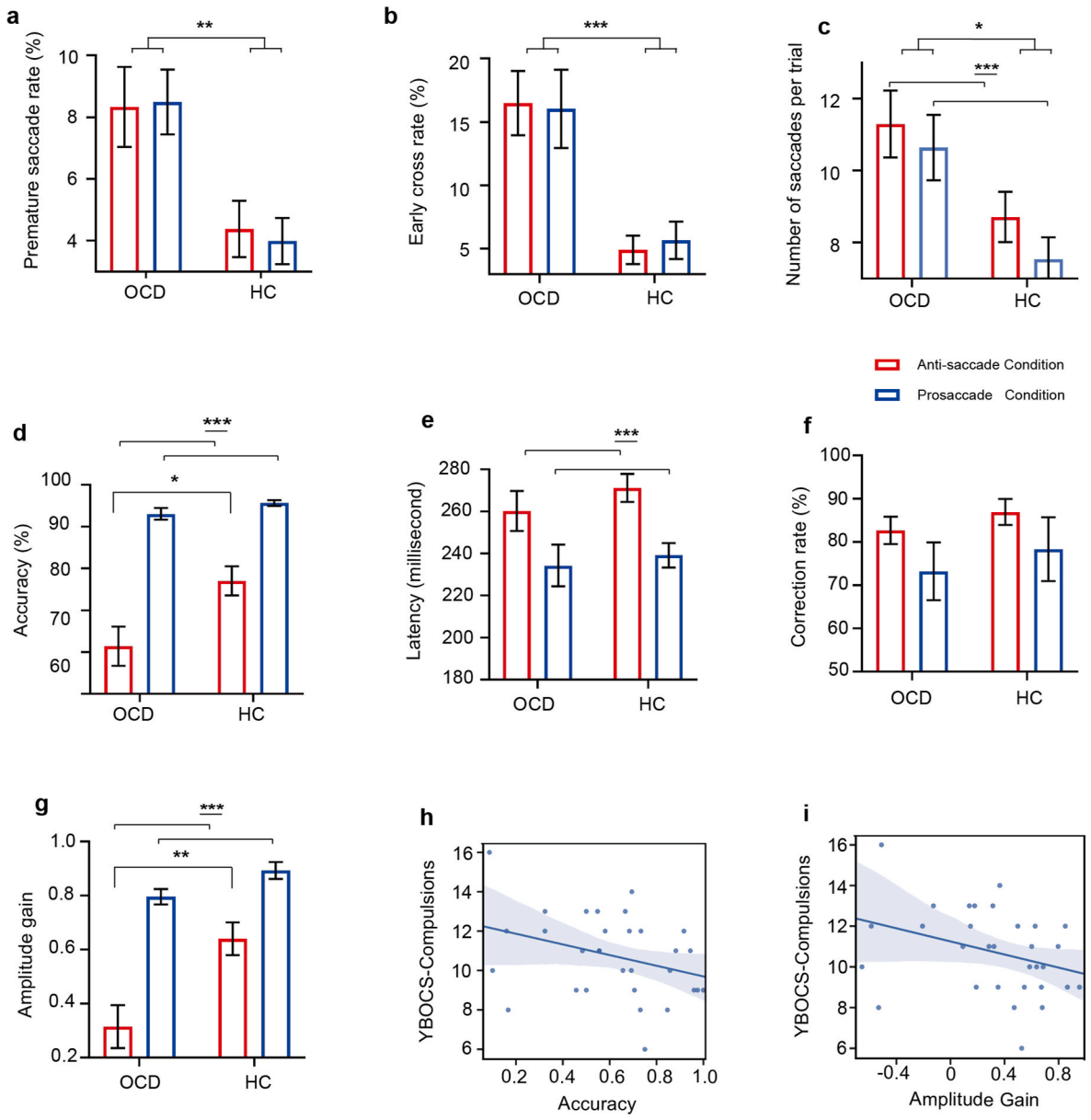

Fig. 3. (**a**–**g**) Multidimensional eye-movement features shown as a function of experimental group and condition. Error bars indicate the standard error of the mean (SEM). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The scatter plots (with best fitting lines) illustrate the individual compulsion score of OCD as a function of the accuracy (**h**) and the amplitude gain (**i**) in the anti-saccade condition. Aterisks with short underline indicate significant main effects of condition.

Table 2
Mean value with the standard deviation (SD, in bracket) of the eye-movement features in each condition for OCD and HC.

Category	Feature	OCD		HC	
		Anti-saccade	Prosaccade	Anti-saccade	Prosaccade
Oculomotor hyperactivity	Early premature saccade rate	0.08 (0.07)	0.08 (0.06)	0.04 (0.05)	0.04 (0.04)
	Early crosses rate	0.16 (0.14)	0.16 (0.17)	0.05 (0.06)	0.06 (0.08)
	Number of saccades per trial	11.30 (5.18)	10.64 (5.07)	8.71 (3.96)	7.53 (3.47)
Oculomotor efficiency	Accuracy	0.61 (0.26)	0.93 (0.08)	0.77 (0.20)	0.96 (0.04)
	Latency (in millisecond)	260.27 (52.76)	234.32 (55.41)	271.25 (38.15)	239.18 (32.78)
	Correction rate	0.83 (0.17)	0.73 (0.32)	0.87 (0.17)	0.78 (0.38)
	Amplitude gain	0.31 (0.44)	0.79 (0.16)	0.64 (0.34)	0.89 (0.18)

3.4. Classification results

The classifier trained with the OH features showed a mean prediction accuracy of 68.0%, 95% CIs [67.95%, 68.05%] (Fig. 4a). The classifier trained with the OE features showed a mean accuracy of 64.61%, 95% CIs [64.54%, 64.68%]. The classifier trained with combined features showed a mean accuracy of 68.48%, 95% CIs [68.41%, 68.54%]. Further permutation-based significance testing showed that the OH prediction accuracy was higher than the OE prediction accuracy, $p <$ 0.001, but was not significantly lower than the prediction accuracy

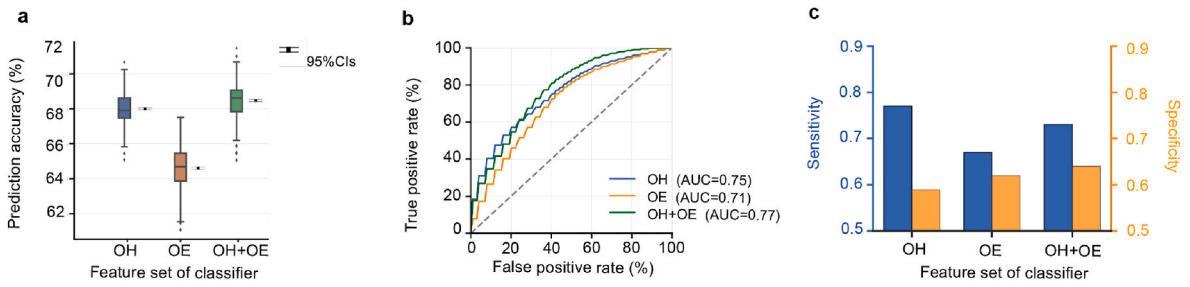

Fig. 4. Classification results (**a**) The prediction accuracies based on the features of oculomotor hyperactivity (OH), oculomotor efficiency (OE) and the combined features (OH + OE), respectively. Outliers are indicated as dots beyond the whiskers. 95% Confidence Intervals are displayed as ranges beside whiskers. (**b**) Mean receiver operating characteristic (ROC) curves of the three classifications. The area under the ROC curve (AUC) indicates the ability to distinguish between the two groups of participants. The dashed grey line represents random chance. (**c**) The Sensitivity (blue) and Specificity (orange) of the three classifications.

based on all features combined, $p = 0.072$. The prediction accuracy based on all features was also higher than the OE prediction accuracy, $p < 0.001$ (Bonferroni-corrected). These results suggested that OH features had higher predictive power than OE features in distinguishing OCD from HCs. Although the combination of all features showed the highest predictive power, adding OE features did not significantly increase the predictive power of OH features.

The mean receiver operating characteristic (ROC) curves, sensitivities, and specificities of the predictions are shown in Fig. 4. The area under the ROC curve (AUC) indicates the efficiency of distinguishing between the two groups of participants. The classifier trained with the OH features showed a higher AUC (0.75) compared to the classifier trained with the OE features (0.71) in a full range (i.e., no intersection between the two curves, Fig. 4b). Although the combination of all features showed a higher AUC (0.77) than OH, a trade-off between true positive and false positive was observed (i.e., there was an intersection between the two curves). The overall specificity of the OH-based classifier was lower than the combination of OH and OE (Fig. 4c). However, the classifier trained with OH features had a higher AUC than the combination of OH and OE under very low false positives (Fig. 4b). Considering that a strict response criterion is often preferred in clinical diagnosis to reduce false positives, the classifier trained with OH features might be optimal among the three for clinical evaluation.

4. Discussion

Here we developed multiple eye-movement features to show the oculomotor characteristics and their capacity as endophenotypic markers of OCD. The CFA results confirmed our hypothesis that early premature saccades early crosses and the number of saccades reflected the task-general oculomotor hyperactivity, while accuracy, latency, correction rate, and amplitude gain reflected the task-specific oculomotor efficiency. The negative correlation between OH and OE also confirmed that a common inhibitory function governed these two categories of eye-movement features. The greater OH and deficient anti-saccade performance in OCD suggested that OCD had broad deficits in preventing the release of the oculomotor response and in inhibiting the task-interfering response. While both feature categories were effective in distinguishing the two groups, the OH features bear the highest prediction power and efficiency.

Traditional neuropsychological approaches to the impaired inhibitory function of OCD mainly focused on the task-interfering response, revealing more No-Go responses, slower stop-signal reaction times, or lower anti-saccade accuracy (Bari and Robbins, 2013; Chamberlain et al., 2005; Menzies et al., 2008). Consistent with existing evidence (Bey et al., 2018; Lennertz et al., 2012; Narayanaswamy et al., 2021), here OCD showed lowered accuracy and lowered spatial precision (i.e., amplitude gain) than HCs in making anti-saccades. In an extension, we found that the impaired inhibitory function was more broadly in generating motor output. Specifically, OCD showed earlier oculomotor release (e.g., early premature saccades and early crosses) and more frequent outputs (e.g., the number of saccades). These OH features were equally observed in prosaccade and anti-saccade conditions, suggesting a task-general oculomotor hyperactivity that is not specific to the required demand of response inhibition. Although the relatives of OCD were characterized with impaired OE features (e.g., anti-saccade accuracy) (Lennertz et al., 2012), so far OH features have not yet been shown as endophenotypes for the relatives of OCD. The higher rates of early premature saccades and early crosses observed here are consistent with the observation that OCD had more anticipatory saccades than HCs (Spengler et al., 2006). These results can be explained by a common oculomotor hyperactivity due to an impaired inhibitory function. Taken together, these findings suggested that motor inhibition and its dysfunction is broadly related to response control, rather than simply related to the stopping or the inhibition of the task-interfering response (Duque et al., 2017).

The simplicity of the testing demand and the direct measurement of the oculomotor activity have enabled the anti-saccade task to be a widely used tool in investigating the cognitive deficits of mental disorders (Broerse et al., 2001; Hutton and Ettinger, 2006). However, given that the lowered anti-saccade accuracy was observed in different mental disorders, it is unknown if this deficit was related to a hyperactivated oculomotor system or a lack of oculomotor vigor. Although both OCD and depression (Curtis et al., 2001; Sweeney et al., 1998) showed lowered ACC, the former could occur as a result of deficient response inhibition whereas the latter case could occur as a result of anhedonia. The neural substrates in the former case could be the hyperactivated frontal-striatal circuits (Saxena and Rauch, 2000), whereas in the latter case could be the hypoactivity in the dopaminergic reward circuits (Pizzagalli, 2014). This ambiguity thus asks for multidimensional features that can complement and constrain each other. During the anti-saccade, both OCD and schizophrenia patients showed lowered accuracy relative to HCs, but only schizophrenia showed increased latency (Damilou et al., 2016; Spengler et al., 2006). These results suggested that the lowered accuracy in OCD cannot be due to motor hypoactivity, and the juxtaposed oculomotor features can be used to differentiate OCD from other disorders that are critically characterized by negative symptoms such as schizophrenia and depression. Here stronger OH suggested that the lowered anti-saccade accuracy and precision cannot be due to hypoactivated frontal-striatal circuits. Instead, the concurrent OH and OE deficits may point to a common mechanism underlined by hyperactivated frontal-striatal circuits. Moreover, previous studies mainly focused on one or two features alone that can distinguish OCD from other mental conditions. The data-driven machine-learning classification has the advantage of combining multiple features. Although we did not investigate multiple-disorder classifications in the present study, our findings can be informative for future studies on this topic to decide how to combine these features.

Relative to conventional manual measurements, eye movements are more sensitive and contain richer spatiotemporal information to reveal the inhibitory functions of mental disorders. People with alcohol dependence showed lowered anti-saccade accuracy but not impaired stop-signal performance (Quoilin et al., 2018). However, there were inconsistent findings when the individual measurements were independently treated. Empirical studies and meta-analysis showed that the lowered anti-saccade accuracy of OCD was not always observed (Spengler et al., 2006), and the effect sizes also varied among different studies (Bey et al., 2018; Jaafari et al., 2011). The effect size achieved here (15% group mean difference) was medium relative to previous studies (e.g., maximum group difference of 27% in Tien et al., 1992). Regarding the correlation between anti-saccade performance and clinical symptoms, a recent study did not find a correlation (Narayanaswamy et al., 2021), whereas the current study showed a double dissociation in distinguishing groups and predicting the symptoms. While the OH features were more sensitive to group distinction, only the two critical OE features were more sensitive in predicting the compulsion scores. This might help to resolve the discrepancies concerning whether anti-saccade performances were effective endophenotypic markers of OCD. As OCD has been considered a heterogeneous disorder, the domain-general and the symptom-specific markers may be related to different groups of eye-movement features rather than a single feature satisfying both homogenous and heterogeneous predictions.

The OH and OE features might be related to different aspects of the response control system in OCD. The goal-directed response and the habitual response are governed by an action monitoring component (see Robbins et al., 2024 for a recent comprehensive model). While the OE features fit with the imbalance between the habitual response (e.g., prosaccade) and the goal-directed response (e.g., anti-saccade), the OH features might be related to action monitoring. It has been suggested that impaired action monitoring led to repetitive behaviors or tendencies in OCD (Stein et al., 2019; Strauss et al., 2020), which is consistent with the pattern of OH features here such as larger saccade numbers and more premature saccades. As action monitoring represents a more general function of inhibitory control, it may be more related to the homogeneity among OCD individuals to have stronger predictive power of group distinction, but less related to the heterogeneity to predict the severity of symptoms.

The limitation of this study lies in the following aspects. First, although OH and OE abnormalities in OCD may originate from a common neural mechanism (the hyperactivated frontal-striatal circuits), neural evidence still needs to verify this mechanism. One specific step that can be taken is to conduct an fMRI experiment with eye-movement recordings to reveal the common and specific neural substrates of the two categories of oculomotor features. Second, the eye-movement features here are not sufficient for distinguishing OCD from HCs, as the achieved accuracy was around 68%. Although this accuracy was comparable to previous studies with a similar sample size (64–73% for distinguishing between 50 patients with Huntington's disease and 22 HCs in Miranda et al. (2016), 57% in distinguishing 24 patients with Autism Spectrum Disorder (ASD) and 28 HCs in the study (Thapaliya et al., 2018), this would limit the diagnostic power of the eye-movement features as biomarkers in clinical practice. The suggestion is to combine the features with other biomarkers or clinical symptoms to achieve higher efficiency. For instance, a recent study showed that the predication sensitivity increased from 78% to 91% in identifying children with ASD ($n = 146$) after the eye-movement features were integrated with primary care practitioner diagnosis. Third, the multiple eye movement features shown here are not sufficient for being the endophenotypes of OCD, as the heritability and the state-independence (Gottesman and Gould, 2003) of these features have not been evaluated. To address this issue, future studies should include unaffected relatives of OCD and conduct longitudinal experiments.

CRediT authorship contribution statement

Zhenni Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Chen Zhang:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Data curation. **Qihui Guo:** Methodology, Data curation. **Qing Fan:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Lihui Wang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Ethical approval

This study was approved by the Shanghai Mental Health Center Ethics Committee (2021-51). All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Data and code availability

Data and codes have been deposited at OSF, accession code: osf.io/5hfx3.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.11.013.

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