Response-Inhibition Deficits in Obsessive–Compulsive Disorder: An Indicator of Dysfunction in Frontostriatal Circuits

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Abnormalities in the orbital prefrontal cortex and its ventral striatal target fields are believed to be involved in causing obsessive and compulsive symptoms. Lesions to this brain circuitry result in a selective disturbance in suppressing responses to irrelevant stimuli. This disturbance might underlie the apparent inhibitory deficit suggested by the symptomatology of obsessive–compulsive disorder (OCD). Oculomotor tests were administered to 12 medication-free, nondepressed patients with OCD aged 18 to 44 y and 12 matched healthy controls to assess the ability to suppress responses and to execute delayed responses volitionally. Patients with OCD had more response-suppression failures than controls when peripheral visual targets were presented close to central fixation. No significant case–control differences were observed on the delayed-response task. A basic disturbance of neurobehavioral inhibition in OCD may underlie the repetitive behavior that characterizes the illness and be related to abnormalities in orbital prefrontal ventral striatal circuits.

Key Words: obsessive–compulsive disorder, response inhibition, orbital prefrontal cortex, ventral striatum, oculomotor testing

INTRODUCTION

Recently, OCD has been recognized as a severe, highly prevalent, and chronically disabling disorder (Robins and others 1984; Valleni-Basile and others 1994; Hanna 1995). Abnormalities in frontostriatal circuitry are believed to be involved in causing obsessive and compulsive symptoms (Insel 1992). Observations (Pitman and others 1987; Cummings and Cunningham 1992) of increased rates of obsessive and compulsive symptoms in neuropsychiatric disorders that result primarily from basal ganglia disease (that is, Tourette's disorder, Huntington's disease, and postencephalitic Parkinsonism) provide indirect support for this model. Functional neuroimaging studies have demonstrated increased metabolic rates in the head of the caudate nucleus and orbital prefrontal cortex in patients with OCD (Baxter and others 1987; Swedo and others 1989; Rauch and others 1994), providing more direct evidence.

Clinically, patients with OCD are impaired in the natural inhibition of repetitive thoughts and behaviors. In animal models and studies of patients with lesions to the orbital prefrontal cortex (Rosvold and Miskin 1961; Luria 1966; Goodglass and Kaplan 1972; Passingham 1972; Stuss and Benson 1983; Diamond 1990), a selective disturbance in the

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Table 1

Demographic and clinical data from patients with OCD and case-matched normal controls

Variable	Patients with OCD n = 12 Mean ± SD (range)	Normal controls n = 12 Mean ± SD (range)	t^a	P
Age	30.1 ± 9.4 (18 to 44)	30.2 ± 9.0 (18 to 45)	0.07	0.95
Sex				
Male	n = 6	n = 6	—	—
Female	n = 6	n = 6	—	—
Patient socioeconomic status	2.8 ± 1.6 (1 to 5)	2.8 ± 1.3 (1 to 4)	0.00	1.00
Age of onset (years)	21.0 ± 9.2 (11 to 39)	—	—	—
Duration of illness (years)	7.5 ± 10.6 (0.7 to 31)	—	—	—

[a]Paired *t* statistic.

ability to suppress responses to irrelevant stimuli has been demonstrated. More recently, Tien and others (1992) observed an increased rate of response-suppression errors on an antisaccade task in 11 adult nondepressed but medicated patients with OCD compared with 14 controls. Thus a disturbance in the orbital prefrontal cortex and its ventral striatal target fields may have a disinhibitory effect that could underlie the apparent inhibitory deficit suggested by the symptomatology of OCD. To date, however, few studies have determined whether there are disturbances in neurocognitive functions believed to be subserved by frontostriatal circuitry in OCD. Tien and others' (1992) observation of increased antisaccade response-inhibition errors in patients with OCD has not been replicated, and other prefrontal cortical functions were not assessed in that investigation.

In addition to response inhibition, the prefrontal cortex is known to subserve other key behavioral functions including initiating delayed responses (Fuster 1989). To date, it is not known whether the response-suppression function of the prefrontal cortex is selectively impaired relative to other prefrontal cortical functions in OCD. Therefore, we evaluated response-inhibition and delayed-response functions to determine whether there is a selective impairment in inhibitory controls of neurobehavioral processes in OCD. Further, by studying medication-free adults, we were able to examine the cognitive skills subserved by the prefrontal cortex without the potential confounds of medications that act on the central nervous system (CNS).

METHODS

Subjects

Twelve psychotropic medication-free, nondepressed OCD outpatients aged 18.0 to 44.3 y and 12 age and sex case-matched healthy comparison subjects were recruited (Table 1). Ten of the 12 patients with OCD were psychotropic medication-naive. Two had been treated with fluoxetine and 1 with alprazolam, but they had not taken any CNS-active medication for at least 12 mo prior to testing. Diagnoses were determined using a semistructured diagnostic interview, the Structured Clinical Interview for DSM-III-R diagnosis (SCID) (Spitzer and others 1990) (Table 2). Patients and controls had comparable socioeconomic status as measured by the Four Factor Index of Social Status (Hollingshead 1978, unpublished observation) (see Table 1). They also had no history of psychosis, bipolar disorder, anorexia or bulimia nervosa, substance abuse or dependence, neurologic disorders including head injury with sustained loss of consciousness, Tourette's disorder, Huntington's disease, dyskinesia, chronic medical illness, or mental retardation. No subject had had a major depressive episode within 9 mo of testing. All subjects had a minimum visual acuity, either corrected or uncorrected, of at least 20/50. Controls had no history of affective or psychotic disorder in 1st-degree relatives and no 2nd-degree relatives with a history of mania, psychotic disorder, suicide, or psychiatric hospitalization. All subjects gave written informed consent.

Clinical measures

Severity of obsessive and compulsive symptoms was measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman and others 1989) (obsessive symptoms median = 11, 25th percentile to 75th percentile = 10 to 14; compulsive symptoms median = 10, 25th percentile to 75th percentile = 7 to 15), and severity of anxiety was measured by the Hamilton Anxiety Rating Scale (Hamilton 1959) (median = 14, 25th percentile to 75th percentile = 10 to 25). Depressive symptoms were measured with the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) (median = 7, 25th percentile to 75th percentile = 5 to 13). All clinical

Table 2

Comorbid diagnoses of adult patients with OCD

Age	Sex	Comorbid diagnoses
18	M	Dysthymia
19	F	None
20	F	Social phobia, history of separation anxiety disorder
23	F	Generalized anxiety disorder
27	M	None
28	F	None
29	F	Panic disorder without agoraphobia
31	M	Anxiety disorder
35	M	None
42	F	Trichotillomania
43	M	None
44	M	Panic disorder, history of major depression

measures were obtained without knowledge of the results of neurobehavioral testing.

Neuropsychological screening

A brief neuropsychological screening examination was conducted to assess general intelligence (Ammons' Quick IQ Test) (Ammons and Ammons 1962), cerebral dominance (Annett Scale of Lateral Dominance) (Annett 1967), manual dexterity (Grooved Pegboard Test) (Knights and others 1980), and attention (Digit Span subscale from the Wechsler Adult Intelligence Scale—Revised) (WAIS-R) (Wechsler 1981). No significant differences in these measures were observed between patients with OCD and case–control pairs except on motor coordination for the nondominant hand (left) (Table 3).

Neurocognitive testing procedures

Oculomotor paradigms have some advantage for assessing neurocognitive processes, mainly through the relatively reflexive nature of most eye movement activity and by the fact that the brain regions subserving different aspects of oculomotor control have been well delineated in single-cell electrophysiological studies in behaving monkeys (Goldman-Rakic 1987, 1988; Funahashi and others 1989; Funahashi and others 1990; Goldman-Rakic and others 1993) and in human functional neuroimaging studies (Fox and others 1985; O'Driscoll and others 1995; Sweeney and others 1996). Two volitionally controlled saccadic eye movement tests were administered (antisaccade and oculomotor delayed-response [ODR] tasks). A reflexive, visually guided saccade task was administered to confirm that any identified abnormalities in volitionally controlled oculomotor function were not attributable to basic deficits in saccade generation.

Testing environment

All subjects were instructed to get a good night's sleep the night before testing. To prevent distraction by extraneous stimuli, subjects were tested alone in a completely darkened room. This facilitated attention during the antisaccade task and eliminated potential background spatial cues. Because of the administration of task instructions and calibration of eye movement recordings, all subjects were in the dark for approximately 15 min before any of the tasks were administered, allowing for considerable dark adaptation. Test instructions were administered by intercom from an adjacent room. Oculomotor responses were monitored during task performance by a research technician. A comfortable chin rest with head restraints and head strap was used to minimize head movement.

Direct-current electrooculography (EOG) recordings were obtained from each eye (Grass Neurodata 12 Acquisition System [Grass Instruments, Boston, USA]) to monitor a wide extent of the horizontal visual field. Small silver chloride electrodes were placed at the inner and outer canthus of each eye. Electrodes were confirmed to have impedances less than 5 kohms using a Grass EZM5A impedance meter. Data from the right eye were scored unless there were problems with the recording (for example, high noise artifact or signal clipping). Electrodes placed above and below the left eye were used to monitor eye blinks. Stationary targets were presented under computer control at a 1-m distance on an arc with individually addressable light-emitting diodes. Except for the short presentation of the to-be-remembered target locations on the ODR task, the central fixation light was turned off concurrently with the presentation of peripheral targets. The spatial location and timing of the presentation of peripheral cues were unpredictable for all tasks. All tasks were presented to the subjects in the same order: visually guided saccades, antisaccades and ODRs. Rest periods were provided both between and during tasks. Each trial was reviewed for artifact (for example, eye blinks and saccades that took the eyes away from center fixation prior to stimulus presentation). This led to excluding relatively few trials from analyses. For example, all subjects had scorable data on more than 80% of trials on the antisaccade task.

Visually guided saccade task

Subjects were required to move their eyes as quickly as possible toward spatially and temporally unpredictable peripheral targets presented at ± 10, 20, or 30 ° from central fixation. The central cue was presented for an average of 2.0 s (range 1.5 to 2.5 s). All peripheral targets were presented for

Table 3

Neuropsychological data from patients with OCD and case-matched normal controls

Measure	Patients with OCD n = 12 Mean ± SD (range)	Normal controls n = 12 Mean ± SD (range)	t^a	*P*
Ammons' Quick IQ Test	97.0 ± 9.6 (86 to 116)	109.3 ± 20.5 (82 to 140)	1.74	0.13
Annett behavioral handedness	10.5 ± 2.5 (6 to 12)	9.8 ± 2.6 (4 to 12)	0.56	0.59
Grooved Pegboard Test				
Dominant hand time (s)	66.8 ± 3.7 (62 to 72)	63.8 ± 9.6 (51 to 77)	0.73	0.50
Nondominant hand time (s)	72.3 ± 5.7 (65 to 81)	64.3 ± 7.3 (57 to 78)	2.90	0.03
Digit Span scaled score from WAIS-R	11.3 ± 1.6 (9 to 13)	11.3 ± 1.4 (10 to 13)	0.00	1.00

[a]Paired *t* statistic.

1.5 s. We measured the latency, accuracy (error in degrees of visual angle), and peak velocity of reflexive, visually guided saccades. Fifty-four trials were presented.

Antisaccade response inhibition task

The antisaccade task was developed by Hallet (1978) and Guitton and others (1985) and requires subjects to fixate a central cue and then look exactly the same distance but in the opposite direction from peripheral targets presented to the left or right of central fixation. In the present study, targets were presented at ± 8, 16, or 24 ° from center fixation. Thus, for example, if a target appeared 24 ° to the right, the subject needed to move his or her eyes 24 ° to the left. This test requires suppression of the powerful reflexive response tendency to look toward novel peripheral targets. This task is not easy, and we find that very few healthy subjects can perform this task without errors on occasional trials.

The technician started by 1st carefully explaining the task verbally and then having the subject practice 8 trials presented at a slow pace while pointing manually to where the eyes should be focused when targets were presented and explaining why the subject should be looking to specific locations. Subjects were then required to explain the task requirements to the technician, after which they practiced additional trials. Only when it was clear that subjects understood the task was recording initiated. During the testing, subjects were reminded of task instructions after 2 consecutive errors (that is, reflexive glances to the target). We recorded the percentage of trials in which the subject looked toward the peripheral targets (response-suppression failures), and the latency and accuracy of saccades toward the correct location. Antisaccades following response-inhibition failures were not included in analyses of saccade latency and accuracy. The peripheral light was turned off 1.5 s after it was presented, and a "correction" light (where the subject should have been looking) was then presented to provide subjects with ongoing feedback about their performance. A total of 36 trials were presented.

ODR task

Subjects began each trial by fixating a central cue. Peripheral targets were presented for 100 ms at 9, 18, or 27 ° to the left or right of central fixation. Subjects were instructed not to move their eyes to the location of the peripheral target when it was presented, but to remember its location while keeping their eyes on the central cue. After a varying delay (1, 2, 4, or 8 s), the central light was extinguished, which served as the subjects' cue to look to where the peripheral target had been presented. It should be noted that the ODR task also has a response-suppression component required in its execution, because subjects were instructed not to look toward the briefly presented peripheral cues until told to do so. Unlike in the antisaccade task, however, the peripheral targets were presented only briefly, and the central fixation light remained on when the peripheral light was presented, cuing the subjects to keep their eyes focused at that location. These factors reduce shifts of attention toward the to-be-ignored targets. As in the antisaccade paradigm, careful, detailed instructions with slow practice trials were performed before testing was begun. The number of responses to the brief peripheral target presentation (response-inhibition failures) and the latency and accuracy of saccades toward the remembered target locations were recorded. A total of 24 trials were presented.

Eye movement analysis

The data were refined with a finite impulse response filter before any processing of oculomotor data occurred. The filter was designed to process a DC signal with progressively increasing filtering from 16 to 70 Hz to reduce high-frequency noise with a minimum of signal reduction and distortion. Custom programs developed in our laboratory were used to analyze eye movement recordings off-line. The

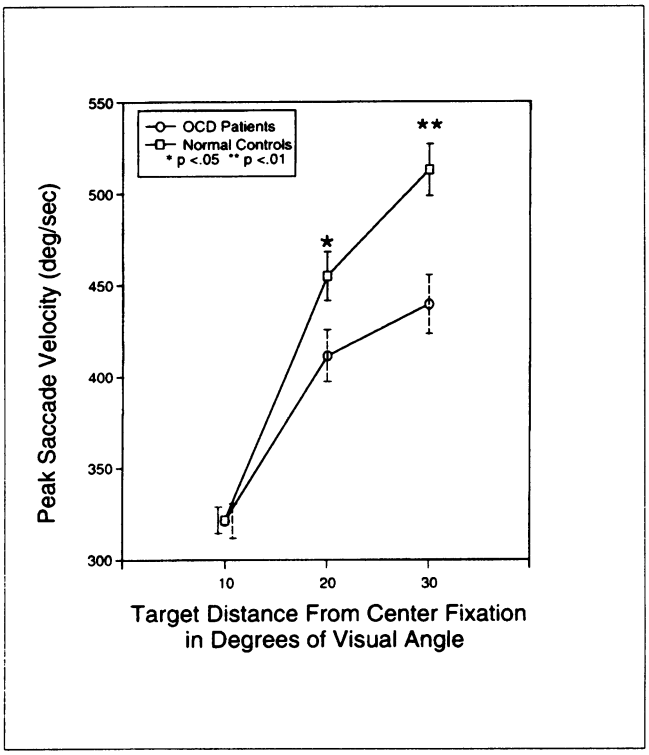

Figure 1. Mean peak saccade velocity for nondepressed, medication-free, young-adult patients with OCD and normal controls performing the visually guided saccade task. Note that patients with OCD have significantly slower peak velocities than controls as the target is displaced farther from central fixation.

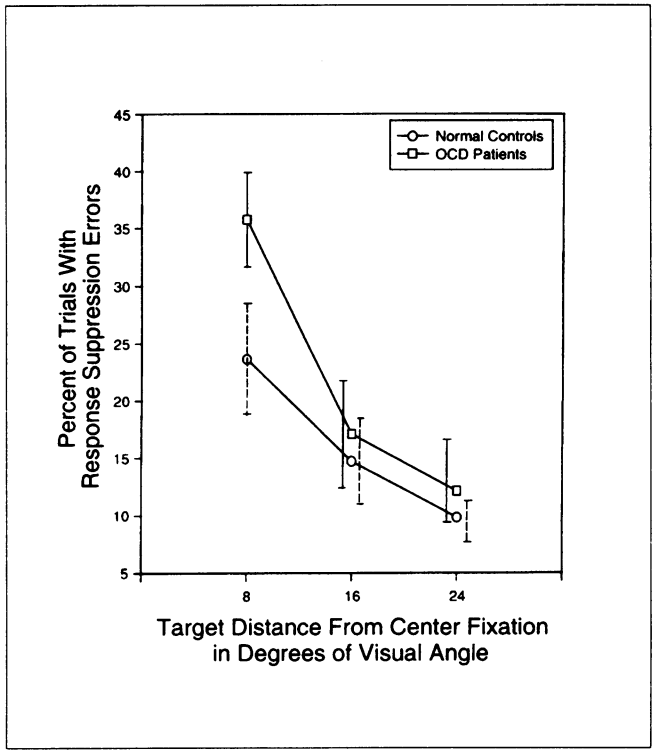

Figure 2. Mean response-suppression failures for nondepressed, medication-free young adults with OCD and normal controls performing the antisaccade task. Note the significant target displacement interaction effect by subject group on antisaccade response-suppression failure rate.

calibration process involved converting eye position recordings from raw voltage data to eye position in degrees of visual angle for each trial independently using data from the time subjects fixated the central fixation cue and the peripheral target location to which subjects were to move their eyes. The technician reviewed the graphically and numerically presented results on each trial and identified blink artifacts and any failures of the software to identify primary saccades. All quantitative assessments of eye movement performance were done without knowledge of identifying information about the subject.

Data analysis

The primary data analyses involved the use of repeated-measure ANOVAs for comparisons of matched case–control pairs on each task. The Tukey Honestly Significant Differences pairwise procedure was used for post hoc group comparisons. Correlations of performance on the eye movement tasks with age, sex, and clinical symptom inventories were also computed. Two-way (sex by diagnostic group) ANOVAs were performed in view of some previous studies suggesting gender-specific abnormalities in OCD (male more impaired than female) (Rasmussen and Tsuang 1986; Luxenberg and others 1988; Tien and others 1992; Blanes and McGuire 1997).

We examined the data for differences in eye movement measurements in the left and right visual fields using repeated-measure ANOVAs in which the main effects of laterality (left versus right) and the interaction of laterality with group were tested separately for each task. Since no significant laterality or interaction effects were observed, data from leftward and rightward saccades were pooled for group comparison purposes.

RESULTS

Visually guided saccade task

Patients with OCD had significantly slower peak saccade velocities on the visually guided saccade task than did healthy comparison subjects ($F[1,11] = 6.03$, $P = 0.03$) (Figure 1). This effect increased as the distance between targets and the point of central fixation increased ($F[2,22] = 9.18$, $P = 0.001$). Patients with OCD did not show any

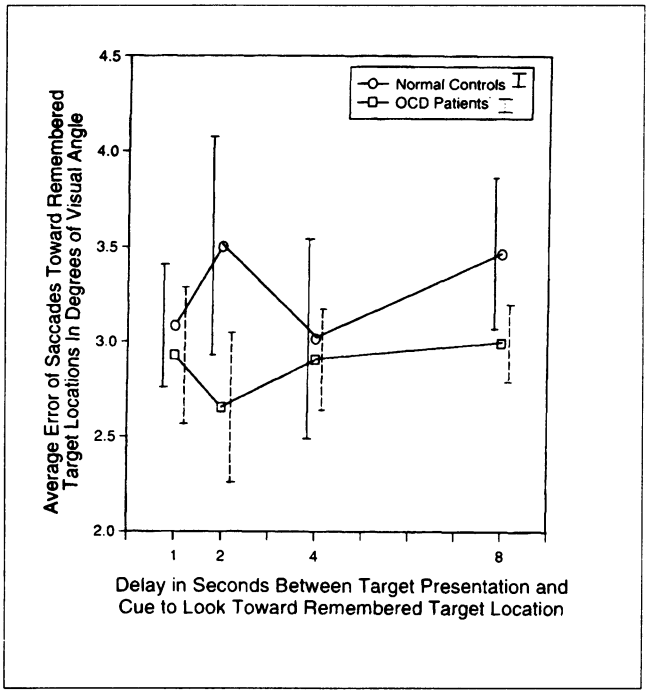

Figure 3. Mean accuracy of saccades to remembered target locations after varying delays for nondepressed, medication-free, young-adult patients with OCD and normal controls performing the ODR task.

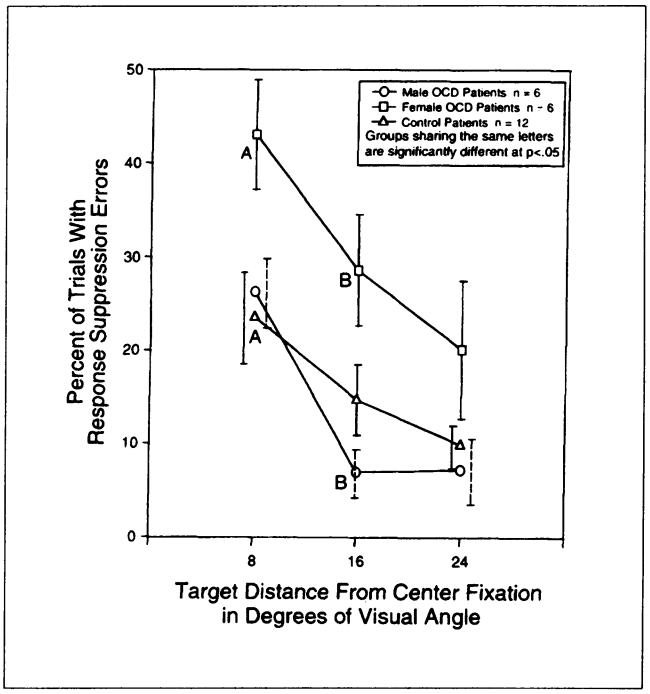

Figure 4. Gender differences in response-suppression failures on the antisaccade task.

abnormalities in saccade latency ($F[1,11] = 0.11$, $P = 0.75$) or accuracy ($F[1,11] = 2.73$, $P = 0.11$).

Antisaccade response-suppression task

A significant target displacement interaction effect was observed by subject group in the antisaccade error rate data ($F[2,22] = 6.94$, $P = 0.005$) (Figure 2), reflecting greater increases in rates of response-suppression failure in patients when targets were presented closer to central fixation. Patients with OCD did not show any abnormality in peak saccade velocities ($F[1,11] = 0.52$, $P = 0.48$), saccade accuracy ($F[1,11] = 0.46$, $P = 0.51$), or saccade latency ($F[1,11] = 0.10$, $P = 0.76$).

ODR paradigm

Response-suppression failures ($F[1,11] = 0.65$, $P = 0.44$), response latencies ($F[1,11] = 1.10$, $P = 0.32$), and peak saccade velocities ($F[1,11] = 0.12$, $P = 0.74$) did not differ between patients with OCD and healthy comparison subjects on the ODR task. It should also be noted that patients with OCD did not make more response-suppression failures on the ODR task at any of the target displacements, even to the targets presented close (± 9 °) to central fixation. The accuracy of saccades toward remembered target locations did not differ between patients with OCD and controls, nor did they decrease when saccades were made after longer delay periods ($F[1,11] = 0.06$, $P = 0.81$) (Figure 3).

Clinical correlations

No significant correlations were observed in patients with OCD between any of the eye movement measurements and severity of OCD symptomatology as measured by the Y-BOCS. Clinical ratings of depression (HDRS), anxiety (HARS), duration of illness, age of onset of illness, socioeconomic status, manual dexterity (Grooved Pegboard Test), and attention (Digit Span subscale from the WAIS-R) were not correlated with any eye movement measure.

Gender

Male subjects were somewhat older than female subjects, although this difference was not statistically significant ($t[22] = 1.47$, $P = 0.155$). A group-by-gender ANOVA was performed with the antisaccade error-rate data (Figure 4). Female subjects with OCD performed significantly more poorly than both male patients with OCD ($F[1,5] = 8.22$, $P = 0.035$) and controls ($F[1,16] = 7.84$, $P = 0.012$) (see Figure 4). Male patients with OCD were not significantly impaired relative to healthy comparison subjects. When we

evaluated response-suppression errors on the antisaccade task as a function of the proximity of targets to central fixation, we found significant gender differences when targets were displaced ± 8 and 16 ° from center fixation but not when targets were displaced ± 24 ° from center fixation. Specifically, female subjects with OCD made more response-suppression errors than controls in response to targets presented at ± 8 (F[1,16] = 5.80, P = 0.02) and 16 ° (F[1,16] = 4.26, P = 0.05). Female subjects with OCD also had more response-suppression failures than male patients with OCD on trials with a 16 ° target displacement (F[1,5] =11.02, P = 0.02) (see Figure 4). There was no significant difference between any of the groups at the 24 ° target displacement, where error rates were consistently much lower. No gender-related differences were observed for saccade accuracy or latency on the antisaccade task, response latency, or accuracy of saccades to remembered target locations on the ODR task, nor were there differences between the sexes for peak velocity, response latency, or saccade accuracy on the visually guided saccade task. Interestingly, the 3 male patients with OCD with a single diagnosis performed comparably to the 3 male patients with OCD with concomitant diagnoses.

DISCUSSION

To our knowledge, this is the 1st cognitive study of nondepressed, medication-free adult patients that is specifically designed to contrast the functional integrity of different domains of prefrontal cortical functions in OCD. These findings replicate, in part, and extend the findings of Tien and others (1992), who demonstrated increased antisaccade response-suppression errors in medicated adult patients with OCD. Our study provides important new data about disturbances in prefrontal neurocognitive functions in OCD by demonstrating that performance in response-inhibition tasks appears to be selectively impaired relative to that observed during spatial delayed-response tasks. Further, the present study documents this without the potential confounding influence of CNS-active medications. Some differences, however, were observed between our study and that of Tien and others (1992). Female patients with OCD in our study showed greater impairment than male patients with OCD on the antisaccade response-inhibition task. In contrast, Tien and others (1992) observed the opposite trend, although female patients with OCD were still impaired relative to controls. Tien and others (1992) also observed increased total antisaccade response failures in patients with OCD versus controls. They did not comment on antisaccade error rates at specific target displacements, but their targets were presented at the 5 to 10 ° range (Tien, personal communication). We observed greater response-inhibition deficits when targets were presented close to central fixation (that is, ± 8 °), suggesting that the deficits in response-suppression ability on the antisaccade task in OCD are largely restricted to foveal or parafoveal stimuli. Thus the results of the present study are consistent with the observation of Tien and others (1992) in indicating response-suppression abnormalities when to-be-ignored targets are presented close to center fixation; further, the results extend this observation by showing that this effect decreases when targets are presented farther from the point of central fixation. Other factors, such as depression and generalized anxiety, did not appear to affect our findings, since there was no significant correlation between anxiety and depression measures and oculomotor response-inhibition errors. Our results support the hypothesis that a deficit in response inhibition is associated with OCD.

Potential relevance for neurobiological models of OCD

Relatively selective disturbances in the orbital prefrontal cortex and its ventral striatal target fields have been identified in neuroimaging studies of OCD (Baxter and others 1987, 1988; Rauch and others 1994). Study of nonhuman primate ventral and dorsal prefrontal cortex has suggested a relative specificity of function for ventral frontostriatal circuitry. Ventral prefrontal cortical regions appear to mediate response-inhibition and -reversal tasks (Rosvold and Mishkin 1961; Passingham 1972; Golden 1978; Fuster 1989; Diamond 1990), while dorsal prefrontal cortical regions appear to be more involved in maintaining spatial information on-line for guiding future goal-directed activity (Goldman and Rosvold 1970; Fuster 1989; Fukushima and others 1990). A loss of inhibitory control over reflexive responses has been observed in humans and nonhuman primates after lesions of the ventral prefrontal cortex (Rosenkilde 1979; Malloy and others 1993), suggesting a critical role for the orbital prefrontal cortex in facilitating suppression of context-inappropriate responses (Rosvold and Mishkin 1961; Luria 1966; Iversen and Mishkin 1970; Goodglass and others 1972; Passingham 1972; Stuss and Benson 1983; Diamond 1990). Thus a basic disturbance of neurobehavioral response inhibition in OCD may underlie the repetitive symptomatic behavior that characterizes the illness. These response-inhibition abnormalities in OCD may be related to failures in frontostriatal circuitry, particularly orbital prefrontal ventral striatal circuits. The fact that patients with OCD exhibited no impairment on the ODR task, believed to be subserved primarily by the dorsal prefrontal cortex, suggests that dorsal prefrontal cortex may be relatively intact in patients with OCD. Moreover, it appears that the closer a target is to center fixation, the more likely it is that subjects will have difficulty suppressing a response to the target, suggesting that this task parameter is manipulating some dimension of antisaccade task difficulty. Functional neuroimaging studies using the appropriate neurocognitive probes are required to clarify the neurobiologic significance of impaired neurobehavioral response inhibition in patients with OCD and how it relates to abnormalities in the orbital prefrontal cortex.

The slower peak velocities observed in patients with OCD on the visually guided saccade task are noteworthy. Saccade velocity is not related to voluntary, purposive, decision-making processes. Instead, the reflexive coordination of the dynamics of saccadic eye movement function is primarily subserved by the brain stem and cerebellum (Waitzman and others 1991). Thus the decreased saccade velocity observed on the visually guided saccade task suggests a disturbance intrinsic to these subcortical regions, a disturbance also suggested by our previous report (Sweeney and others 1992) of abnormal velocities of pursuit eye movements in a different sample of patients with OCD. These data suggest an unusual pattern of decreased output from subcortical regions involved in the generation of simple reflexive eye movements in OCD.

One possible explanation for the decreased peak saccade velocity in OCD is that it may be due to a perturbation of serotonergic modulation of brain stem regions involved in the generation of saccades. Serotonin is the neurotransmitter most implicated in the pathophysiology of OCD. Lesions to the raphe nucleus in monkeys markedly slow saccadic eye movements (Kaneko and Fuchs 1991), and L-tryptophan induces saccadic inhibition (Smith and Prockop 1962; Baloh and others 1982), probably by disinhibiting pause neurons in the raphe (Ashikawa and others 1991). Fluoxetine has been shown to cause a disinhibition of eye movements during non-REM sleep in patients with OCD, probably from a potentiation of serotonergic inhibition of brain stem pause neurons (Schenck and others 1992). Moreover, decreased 5-hydroxytryptophan (5-HT) tone in the raphe decreases saccade velocity, while administration of the serotonergic agonist MK-212 has been shown to increase the velocity of pursuit eye movements in healthy control subjects (Friedman and others 1994). In this regard, the relatively dense serotonergic innervation of ventral prefrontal cortex may contribute to the antisaccade response-inhibition failures observed in patients with OCD by disturbing neuromodulatory processes. It should be noted that there are no direct data on the nature of brain stem or ventral prefrontal cortical 5-HT abnormalities in OCD. Studies with such functional neuroimaging modalities as positron emission tomography (PET) might be conducted to measure regional 5-HT receptor densities to clarify any relations between serotonergic abnormalities and neurobehavioral deficits in OCD.

Gender

The poorer performance of female patients with OCD on the antisaccade response-inhibition task is not consistent with Tien and others' (1992) findings of greater impairment in male patients with OCD. Even more surprising was the fact that male patients with OCD performed as well as controls on this task. A subgroup of patients with OCD has been characterized by male gender, early onset, severe symptoms, neurological signs, and a chronic, refractory course (Rasmussen and Tsuang 1986; Luxenberg and others 1988; King and Tonge 1991; Thomsen 1995; Blanes and McGuire 1997). Female patients with OCD, however, have been shown to exhibit impaired performance on alternation learning tasks relative to controls (Gross-Isseroff and others 1996). Factors such as sex differences in anxiety, depression, OCD symptoms, attention, coordination, socioeconomic status, age of onset, and duration of illness did not appear to account for this gender difference. It should be noted, however, that male subjects were slightly older, on average, than female patients with OCD. Oculomotor function declines with advancing age, although it declines most significantly at ages older than those of subjects tested in the present study. Given the small sample size in this study, as well as in that of Tien and others (1992), caution in interpreting the significance of these gender differences as they relate to the pathophysiology of OCD is indicated.

CONCLUSIONS

A basic disturbance of neurobehavioral response inhibition in OCD may underlie the repetitive symptomatic behavior that characterizes the illness. Such neurobehavioral response-inhibition abnormalities in OCD may be related to failures in frontostriatal circuitry, particularly orbital prefrontal ventral striatal circuits. Our data failed to confirm that males were more impaired than females—in fact, they suggest that females with OCD may be more impaired in their response-inhibition abilities, particularly on more difficult response-inhibition tasks. Disturbances of orbital prefrontal cortex may disrupt neurobehavioral response inhibition and thereby interfere with ongoing purposive behavior in patients with OCD. Further, these disturbances may be related to the emergence of symptoms such as disinhibited ego-dystonic ritualistic behavior associated with this illness.

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