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Effects of amphetamine on saccadic eye movements in man: possible relevance to schizophrenia?

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The antisaccade task can be used to test the voluntary control of saccadic eye movements (SEMs). In many disorders with postulated hyperdopaminergic neurotransmission, there are reports of abnormalities in SEMs. To further investigate this, the role of dopamine in SEMs, performance on an antisaccade task was examined in subjects with a history of amphetamine use (a dopamine releaser and reuptake inhibitor). A prospective design was employed in a teaching hospital setting. Six subjects (five males) with a history of amphetamine use were compared to 24 normal controls. None of the subjects were using any other substances, except alcohol and nicotine, as determined by urine screening, which we believe limited the sample size. For subjects who used amphetamine before the task, the presence of amphetamine was confirmed by urinalysis. All subjects completed the antisaccade task. Both error rates and latency rates during the antisaccade task were compared between the amphetamine users and controls. The amphetamine users had significantly increased error rates and latencies. These results may suggest that increased error rates and latencies during antisaccade tasks may be due to increased dopamine transmission, which is similar to the findings in schizophrenia.

Key words: antisaccade; amphetamine; dopamine; saccadic eye movements

Introduction

Saccadic eye movements (SEMs) can be observed when a subject looks at a target light that is moving rapidly. These movements provide quantifiable information about sensory-motor integration. In particular, the antisaccade task is used to investigate voluntary control of SEMs. In the antisaccade task, a target light is presented on one side of fixation and the subject is required to look in the opposite direction at an approximately equal distance from fixation. That is, the subject must over-ride the natural tendency to look at that target and instead exercise endogenous control of attention in order to look away from it. Because the exogenous control of attention by the light is powerful, subjects typically make saccades towards the light on some trials; these inappropiate saccades are judged as errors.

Abnormalities in an antisaccade task have been demonstrated to be independent of abnormalities in saccade tasks. For example, patients with lesions to the dorsolateral prefrontal cortex have difficulties in antisaccade task, but not with saccade simple tasks (Guitton et al., 1985). In addition to the dorsolateral prefrontal cortex (DLPFC), brain imaging studies in humans have identified the prefrontal eye field and the supplementary eye field as areas involved in the activation of voluntary saccades (O’Driscoll et al., 1995; Sweeney et al., 1996; Schlag-Rey et al., 1997). Recently, neural models have also led to the hypothesis that the control of the eye movements may involve the superior colliculus (Everling et al., 1997).

Patients with schizophrenia have normal SEMs on simple tasks (Levin et al., 1982) but have higher error rates and longer latencies than controls on antisaccade tasks (Thaker et al., 1989; Fukushima et al., 1990; Sereno and Holzman, 1995). In patients with schizophrenia treated with clozapine, risperidone or sulpiride, saccadic eye movements are also reported to be abnormal (Reveley et al., 1996). Error rates and latencies in antisaccade tasks are also significantly increased in advanced parkinsonian patients; these rates are positively correlated with the presence of bradykinesia (Gibson et al., 1987; Kitagawa et al., 1994). Additionally, in Huntington’s disease and Tourette’s syndrome, consistent findings indicate that patients have an inability to suppress reflexive glances and have delayed initiation of voluntary saccades (Reveley et al., 1994, 1995; Lasker and Zee, 1997). Because these disorders have been linked to an imbalance in brain hyperdopaminergic states, we hypothesized that the reported SEM abnormalities may be due to disturbances in dopaminergic neurotransmission. Accordingly, we hypothesized that drugs that alter brain dopamine activity would increase SEM abnormalities. One such drug is amphetamine, which is a dopamine releaser and inhibits dopamine reuptake. Thus, to test the hypothesis, we investigated the impact of amphetamine use on SEMs. Data from six subjects with a history of amphetamine use were compared to that of 24 control subjects.
Methods

Amphetamine users
Six subjects (five males) with a history of amphetamine use were tested. Subjects stated that the last amphetamine self-administration was $8.5 \pm 1.4$ h (mean $\pm$ SD) before the SEM test. The presence of amphetamine was confirmed by urinalysis in all experimental subjects. None of these six subjects were using any other substances (excluding alcohol and/or nicotine, which were not at a level of ‘substance abuse’), as self-reported and confirmed by negative urine screening. Also, none of the subjects had any clinically symptomatic neurodevelopmental disorders or mental retardation.

Control group
There were 24 control subjects (16 males). All were in good physical health and all measures were in the normal range on complete medical and neuropsychiatric evaluations. All of the control subjects were medication- and drug-free during the test and had no previous diagnosis of alcohol or drug abuse.

Measurement of saccades
All subjects were tested as described in a previous study (Reveley et al., 1996). After calibration, all subjects were initially tested using the ‘random task’ to ensure that they had the ability to understand the experiment. The target display consisted of four red light emitting diode (LED) targets (diameter 0.25”) placed at $\pm 7.5^\circ$ and $\pm 15.0^\circ$ on either side of the central fixation LED. The LED targets were only visible when illuminated. A buzzer was located directly centred behind the subject’s head. The distance between the seat and the screen was 1.5 m. Head movements of the subjects were constrained by the use of an adjustable head rest. The stimuli and data collection were controlled by a computer using software especially written for this purpose (GAMTech, Germany).

In the antisaccade task, subjects were instructed to inhibit a reflex eye movement towards a peripheral target light and instead generate a movement of equal magnitude in the opposite direction. Errors were recorded when the subjects failed to suppress reflexive saccades towards the target. Error rates were calculated as the percentage of trials on which errors occurred out of the total number of saccadic eye movements. Latency was computed as time taken to complete correctly performed saccades and was expressed in milliseconds.

Analysis of urine amphetamine
A standard immunoassay method (Syva, Leicester, UK Ltd) was used to determine levels of amphetamine derivatives in urine. Positive screening results were confirmed by an additional thin layer chromatography method (Toxilab, Leicester UK Ltd).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Correct response latencies and error rates obtained during the antisaccade task</th>
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<tbody>
<tr>
<td></td>
<td>Correct response latency (ms)</td>
</tr>
<tr>
<td>Controls</td>
<td>$390 \pm 46$</td>
</tr>
<tr>
<td>Amphetamine users</td>
<td>$635 \pm 157^*$</td>
</tr>
</tbody>
</table>

*Data are mean $\pm$ SD. $p<0.01$ (Student’s t-test) versus controls.

Results

The mean age of the amphetamine-using subjects was not significantly different from that of the controls, 32.7 $\pm$ 6 versus 29.5 $\pm$ 10 years, respectively. Error rates and latencies of correct anti-saccade performance were significantly increased in amphetamine users as compared to control subjects (Student’s t-test, $p<0.01$). Subjects taking amphetamine made nearly six times as many errors as control subjects, making inappropriate saccades towards the light on nearly three-quarters of the trials (Table 1). On those trials when the amphetamine users did respond correctly they were slower than controls, taking approximately 1.6 times as long to respond (Table 1).

Discussion

These results support the hypothesis that increased error rates and latencies of correct antisaccades in schizophrenia, Tourette’s syndrome, and Huntington’s disease may be due to the increased dopaminergic neurotransmission in the mesofrontocortical dopamine pathway. Prior to the test, all subjects had consumed amphetamine, a drug that enhances dopaminergic neurotransmission. Furthermore, as chronic amphetamine intake results in progressively increased (‘sensitized’) dopamine activity (Robinson and Becker, 1986; Kalivas et al., 1993) and all experimental subjects were habitual amphetamine users, it can be assumed that dopamine activity was elevated in those subjects relative to controls.

The most likely neuroanatomical basis for these abnormalities is the functional network between the basal ganglia and the cerebral cortex, more specially the dorsolateral prefrontal cortex. This possibility is supported by evidence from animal neurophysiological, human lesion, and neuroimaging studies (Pierrot-Deseilligny et al., 1991). It is hypothesized that increased dopaminergic activity in the prefrontal cortex may disrupt control over voluntary eye movements by altering activity in a fronto–striatal–nigral projection, hence decreasing activity in a tonically inhibitory projection to the superior colliculus from the substantia nigra, pars reticulata. A compatible interpretation is based on the observation that dopamine is inhibitory in the prefrontal cortex, as indicated by the fact that stimulation of the dopamine neurons of the ventral tegmental area causes a decrease in the firing rates of neurons in the prefrontal cortex. Hence, increased error rates and latencies in ‘hyperdopaminergic states’ may reflect a decrease in prefrontal cortical activity. However, there are limitations to this proposed mechanism, one of which is certainly the sample size. Given the fact that the average
amphetamine use was 8.5 h prior to testing, it could be argued that the data of the study may not necessarily reflect the acute effect of amphetamine. Indeed, these subjects were all chronic users who had been taking amphetamine at varying doses and periods, and the data may reflect the chronic changes. However, at the time of the test, none of the amphetamine users appeared to be in a withdrawal or ‘crash’ phase. They were clearly able to understand the instructions. One needs to rule out the possibility that chronic amphetamine use is associated with damage and down-regulation to brain dopaminergic systems and that this parallels the hypodopaminergic state which has been postulated to occur in the frontal cortex (Weinberger et al., 1992). Also, we have not had the opportunity to determine the error rates and latencies of ‘amphetamine users’ prior to amphetamine use (premorbid functioning) and the effect of these premorbid error rates on saccadic eye movements. Furthermore, It is possible that the functioning and differences in character (e.g. impulsivity), all of which might be associated with an inability to restrain saccadic eye movements.

Further studies with larger sample size and detailed data are required to confirm these findings.

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