Drug effects on ocular behavior

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ABSTRACT

Ocular behavior measures were measured with a prototype device, the Fitness Impairment Tester (FIT), following ingestion of four different drugs: codeine (a narcotic-analgesic), alprazolam (a CNS depressant), d-amphetamine (a CNS stimulant), and cannabis. The FIT provides 100 measures of ocular performance that are derived from tests requiring saccadic eye movements in response to a 'jumping' target, smooth tracking movements in response to smoothly moving target, steady fixations (vs nystagmus) in response to targets appearing in the peripheral field, pupil dilation and constriction in response to changes in background luminance, and convergence of the two eyes in response to a target moving towards the observer. The present study analyzed the data obtained from a sample of self-proclaimed drug users after administrations of placebo, low, and high dosage levels of the four different drugs, and compared their performance to non-dosed normal subjects. The sensitivity and specificity of the over 100 ocular measures were assessed in terms of their ability to distinguish the presence of drugs (a) relative to placebo, and (b) relative to the ocular performance of the normal (non drug-using) population. Using logistic regressions, it was possible to distinguish between drug dosed and placebo rinsed regular drug users, and between drug-dosed regular users and normal subjects at above chance levels relative to two drugs: alprazolam and cannabis. Examination of the specific tests that entered the logistic regression indicates that (1) most measures are not sensitive to the drug impairments studied, (2) the tests and measures that are, are not the ones predicted from the literature review.

INTRODUCTION

Drug recognition experts (DRE's) are police officers who are specially trained to detect drug impairment on the basis of observable signs and symptoms such as blood pressure, pupil response to light, and eye movements in response to a moving target. The rationale for these tests has been that numerous studies have noted the effects of tranquilizers, antidepressants, antispasmodic, hypnotic, anesthetic, CNS stimulants and depressants, and narcotic analgesic drugs on eye movements and pupil size and reflexes. The DREs measures, however, are based
on subjective observations and manual recording of the data and as such are subject to large inter- and intra-observer variations. In addition, it is not clear that the specific measures used by the DREs are the most closely associated with the different drug impairments.

The purpose of this study was to provide (1) a more objective method for both observing and recording the ocular data, and (2) evaluate many additional ocular measures that, because of technological limitations, have not previously been evaluated relative to their relationship to drug-specific impairments. The first benefit of objective methods derives from their ability to reduce individual differences in levels of training, eliminate bias in observations, and increase accuracy in scoring performance. The second benefit of automated devices, is that they can accurately measure aspects of performance that are not measurable manually. For example, a potentially useful measure is the saccadic latency and peak saccadic velocity in moving towards a target. Research on the effects of alcohol on these measures has shown a dose-related decrease in the velocity of saccadic movements (without necessarily a reduction in fixation accuracy) (e.g., Jantti, Lang, et al., 1983; Lehtinen, et al., 1979), and a dose related increase in the latency or reaction time to initiate saccadic movements (e.g., Baloh, et al., 1979; Jantti et al., 1983; Levett and Jaeger 1980; van S c h r e m a c k, Gieschke, Schoemaker, Pieters, Kroon, Breimer, and Cohen 1993).

Based on the literature review we expected to obtain the following effects for each drug:
2. Alprazolam (Tranquilizer/CNS Depressant). Reduced peak velocity of saccadic eye movements (Griffith, Marshall, and Richens, 1984; Aschoff, 1968) and increased saccadic latency (Aschoff, 1968).

METHOD

Subjects
The subjects in this study were 61 paid volunteers, who (1) were self-admitted regular users of the study drugs, (2) assured the staff that they never had, nor did they currently intend to seek substance-abuse treatment, and (3) judged to be in good health.
Study Design
Each of the subjects was recruited as an in-patient for a period of up to three weeks. Within that period each subject was tested with only one of the four drugs on six sessions, separated from each other by at least 48 hours. The first session was used to screen subjects who may have a negative reaction to the high dose level of that subject's drug. In the following 6 sessions each subject was orally administered all three drug levels twice: Placebo, low dose and high dose. The order of the dose levels was counterbalanced between subjects. The two dose levels for codeine were 60 and 120 mg (in capsules). For alprazolam they were 1 and 2 mg (in capsules). For d-Amphetamine sulfate they were 12.5 and 25 mg (in capsules). And for marijuana they were 16 mg and 32 mg THC (in two cigarettes). The dose levels of did not to exceed the maximum daily therapeutic dose. Oculometer performance was measured in a 'double blind' design both prior to and after dosing.

The Fitness Impairment Tester - an Overview of the Tests
The Fitness Impairment Tester consists of an enclosed vision tester that is linked to a personal computer that runs the tests and records the subject's eye movements (at a sampling rate of 800 Hz), and pupil size (at a sampling rate of 60 Hz). It automatically administers a series of 11 tests that yield 100 measures of performance. The tests measure convergence of the two eyes on a point moving in towards the viewer, pupillary constriction in response to light, and tracking and saccadic eye movements in response to a moving target. The tests are:

1. Instrument Calibration (CAL). Also used to record saccadic eye movements in response to a target that 'jump' back and forth from right to left.

2-3. Slow Smooth Target Movement to the Left (SML22) and Right (SMR222). Records pursuit tracking movements in response to a target moving from the center to the left at 22 degrees/sec.

4-5. Fast Smooth Target Movement to the Left (SML41) and Right (SMR41). These tests are identical to the second test in all respects except that the target speed is 41 degrees/second.

6-7. Step and Dwell to the Left (STPL) and Right (STPR). These tests record saccadic movements in response to a target that jumps to the left and right from 20 degrees off-center to 45 degrees in 5-degree intervals.

8. Step and Dwell Up (STPU). This test is identical to the previous one except that the target jumps in 5 degree increments up along the vertical arc up to an angle of 35 degrees.
9. Convergence (CONV). The test records convergence of the two eyes in response to a target moving towards the subject's eyes at 5 cm/second until it gets to 7.5 cm from the bridge of the nose.

10. Pupil Light Test (PLT). Recorded the pupil constriction in response to three successive steps on increasing background luminance from 5-ft-L to 15 ft-L.

11. Pupil Flash Test (PFT). In this test the background lights up at a high intensity (15 ft Lamberts) for a brief flash of 100 milliseconds. The purpose is to measure the maximal pupillary constriction.

Analytical Approach
To assess true drug ingestion effects, the best measure would be one that is based on each subject's change in performance. This would imply deriving for each subject a difference measure of \( D_i = X_i(\text{before}) - X_i(\text{after}) \), where \( X_i \) is the performance on Test Measure \( i \). Once \( D_i \)'s are calculated for each subject on each measure, the true drug effects can be assessed by comparing the group \( D_i \)'s under the dosing conditions with \( D_i \)'s under the Placebo conditions. Unfortunately, the \( D_i \) measure, which has the benefit of both (1) theoretical validity, and (2) elimination of individual differences in their baseline performance, is totally useless in the context of this study. This is because in real-life assessment, there is only one measure for each subject, and we do not know which one it is: the \( X_i(\text{before} - \text{meaning not under the influence}) \) or the \( X_i(\text{after} - \text{meaning under the influence}) \). Consequently a weaker test must be employed; one that compares the group's performance after a specific drug dosing to its performance after the ingestion of the Placebo. This method increases the within-condition variance and therefore requires greater drug dosing effects to distinguish between drug-dosed and placebo-dosed subjects. However, the results obtained are no less valid, since the use of the Placebo condition as a bench-mark for the drug effects eliminates the non-specific psychological effects that are not due to the true physiological effects of the drug.

RESULTS AND DISCUSSION

Identification of Candidate Ocular Measures
The first step was to determine which measures - within each of the 11 FIT tests - were the most powerful in discriminating between performance in the placebo post-dosing condition and performance in the drug post-dosing conditions (with the low and high doses combined). The measures were selected based on logistic regression (SAS PROC LOGISTIC), using a relatively liberal criterion for inclusion of \( p=0.3 \). Classifying observations according to a logistic model which is derived from the same observations leads to biased results. Therefore, one attractive feature of this procedure is that it uses the 'jackknife' approach in the
classification process. In this method, some cross-validation of the logistic function is provided by removing each observation to be classified, one at a time, from the data from which the classification function is derived. Thus, each trial is classified using a slightly different function from the one that is derived from the complete data set. The function derived from the complete data set is then the one recommended for use on a new independent observation.

The results of the logistic regression analyses showed that (1) not all tests yielded significant measures (even at a liberal criterion for inclusion of $p=.3$), and (2) the Convergence test failed to yield significant measures for all four drugs. The tests that were significant can be considered as the most discriminating measures of true drug effects since they are sensitive to the dosing relative to the placebo effect, rather than relative to the performance before drug administration in which both the subject and the examiner are aware of the true (i.e., before dosing) situation.

The next step was to determine for each drug, which combination of the statistically significant measures, when pooled together, provides the most sensitive and specific discrimination between the dosed and non-dosed conditions. Because of the small number of subjects in each drug group, it was necessary to combine performance of the subjects from all the drug groups for the Placebo condition, and to combine performance for both drug dosing conditions (High and Low doses) in each drug category. The logistic regressions that were derived based on the differences between the placebo and drug-dosed, were then cross validated by testing their ability to discriminate these same drug-dosed subjects from the Normal population. In a similar manner, logistic regressions were also developed and cross validated by proceeding in the opposite direction. This was done by using the same measures used in the first regressions to calculate a regression function derived from comparing the performance of the drug-dosed subjects to the performance of the normal population. Then this function was cross-validated by testing its ability to distinguish between performance under the drug-dosed condition and performance under the placebo-dosed condition.

The main results are presented in the table below in the following terms:

- Sensitivity. The probability that the test will detect the specific drug impairment.
- Specificity. The probability that the test will reject non-drug-impaired subjects.
- False Alarms. The probability of incorrectly classifying a non-drugged person.
- Misses. The probability of incorrectly classifying a drugged person.
Summary of the discrimination ability of the FIT-1000 measures to detect drug effects

<table>
<thead>
<tr>
<th>Cross Validity</th>
<th>Codeine</th>
<th>Alprazolam</th>
<th>Amphetamine</th>
<th>Cannabis</th>
</tr>
</thead>
<tbody>
<tr>
<td>To Normals:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.00</td>
<td>0.30</td>
<td>0.04</td>
<td>0.47</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.84</td>
<td>0.67</td>
<td>0.61</td>
<td>0.66</td>
</tr>
<tr>
<td>False Alarm</td>
<td>0.00</td>
<td>0.05</td>
<td>0.01</td>
<td>0.15</td>
</tr>
<tr>
<td>Misses</td>
<td>0.32</td>
<td>0.35</td>
<td>0.35</td>
<td>0.13</td>
</tr>
<tr>
<td>Concordance (%)</td>
<td>60.5</td>
<td>77.6</td>
<td>72.6</td>
<td>88.2</td>
</tr>
<tr>
<td>To Placebo:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.00</td>
<td>0.65</td>
<td>0.09</td>
<td>0.73</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.68</td>
<td>0.44</td>
<td>0.83</td>
<td>0.67</td>
</tr>
<tr>
<td>False Alarms</td>
<td>0.05</td>
<td>0.39</td>
<td>0.06</td>
<td>0.18</td>
</tr>
<tr>
<td>Misses</td>
<td>0.55</td>
<td>0.15</td>
<td>0.74</td>
<td>0.13</td>
</tr>
<tr>
<td>Concordance (%)</td>
<td>80.7</td>
<td>96.9</td>
<td>83.2</td>
<td>97.5</td>
</tr>
<tr>
<td>Tests with Significant measures in the logistic regression</td>
<td>SML22 PFT</td>
<td>PFT STPU</td>
<td>CAL SMR22 STPU</td>
<td>SML22 SMR22 SMR41 STPL STPU</td>
</tr>
</tbody>
</table>

From the summary table above, it is readily apparent that the FIT can provide a reasonable tool for the detection of alprazolam and cannabis. The overlap between the drugs in the measures that best predicted their involvement was not very large. Alprazolam effects were manifested primarily in measures of pupillary reactions to light, accuracy of vertical saccadic eye movements, and maximum gaze angle in smooth pursuit tracking. Cannabis effects were manifested primarily in impairments in smooth pursuit tracking and reduced stability of fixations in lateral saccadic eye movements (The measures included in the logistic regressions of codeine and amphetamine are irrelevant because of their poor discriminatory capability).
CONCLUSIONS AND RECOMMENDATIONS

1. The FIT provides a better than chance classification for alprazolam and cannabis impaired subjects.
2. Only a small subset of the tests used and the measures recorded with the FIT are useful predictors of drug impairment and these are typically the more reliable measures.
3. Additional studies should evaluate the:
   - The relationship between the oculometer data and the DREs’ subjective evaluations.
   - The source of discrepancies in the responses of the two eyes to the same stimulus target.
   - Long-term drug effects that distinguish between regular drug users and normal non-users.
   - The relationships between drug-related ocular impairments and the cognitive impairments.

REFERENCES


Jantti, V., Lang, A.H., Keskinen, E, Lehtinen, I., and Pakkanen, A. Acute effects of


