The effects of clonidine, idazoxan and noise stress on saccadic eye movements

[1]Andrew P Smith, Nicholas J Coupland[2], Jayne E Bailey[3], David J Nutt[4]

[1] Cardiff University, School of Psychology, Cardiff, UK (corresponding author)
[2] University of Alberta, Department of Psychiatry, Canada
[3] University of Bristol, UK
[4] Imperial College London, Neuropsychopharmacology Unit, UK

Corresponding author's e-mail address: smithap@cardiff.ac.uk

ABSTRACT

The antihypertensive α2-adrenergic receptor agonist, clonidine, has been shown to slow saccadic eye movements. Noise has been shown to reverse clonidine-induced impairment of sustained attention. The present study aimed to test whether the effects of clonidine on saccades and blood pressure were blocked by the selective antagonist, idazoxan, and whether the effect of clonidine was modified by noise. Seventy-six healthy male participants were administered either clonidine 200µg, idazoxan 40mg, the combination of clonidine 200µg plus idazoxan 40mg, or placebo orally, in a double-blind, parallel group design. Half of the participants, balanced across drug treatment groups, were also administered 80dB white noise via headphones. At baseline and on three occasions after drug administration participants performed a visually guided saccade task. Cardiovascular parameters were also measured on each occasion. Clonidine significantly decreased saccade peak velocity compared with placebo. Idazoxan did not show an intrinsic effect on saccades, but fully antagonised the effects of clonidine. Noise had little effect on the speed of eye movements suggesting that the activation of other neurotransmitter systems may underlie the effects of noise on sustained attention.

INTRODUCTION

One of the explanations of effects of noise on cognitive performance has been in terms of arousal [1, 2, 3]. Initially, loud noise increases arousal which can account for some of the improvements found in certain studies [1]. More prolonged exposure leads to over-arousal which can then be associated with impaired performance and/or a subjective state of increased fatigue. Some of the strongest

evidence for the arousal theory of noise comes from studies of the antagonistic effect of noise when a person has a low level of arousal such as that produced by sleep deprivation [4, 5]. Several studies have examined the effects of noise on cognitive performance and on peripheral catecholamines as indices of arousal [6, 7]. Plasma and urine noradrenaline and adrenaline were increased by noise [8], but not consistently [9]. However, peripheral measures have many limitations as indices of central noradrenergic function [10]. Smith and Nutt [11] examined the effects of noise following a clonidine challenge which produced an effect resembling sleep deprivation. Performance of a sustained attention task was impaired by the clonidine and this effect was reversed by noise.

The present study examined the effects of clonidine and idazoxan on saccadic eye movements when the person was in quiet or noise. Previous research has shown that the α 2-agonist clonidine, reduces saccade peak velocity, but does not alter saccade latency or accuracy [12]. The α 2-antagonist idazoxan prevents small decreases in saccade peak velocity that occurr during quiet rest in the placebo conditions [12]. α 2-adrenoceptor agonists and antagonists modulate arousal through changes in noradrenergic neuron firing. α 2-agonists decrease noradrenergic neuronal firing, noradrenaline release and behavioral and electrophysiological indices of arousal. α 2-antagonists block these effects, but can also produce the opposite effects when administered alone. Saccades are rapid eye movements that direct gaze to a new position, in response to an externally or internally generated target. Despite extensive preclinical and clinical research into the neural bases of eye movement control, there has been relatively little investigation of the neurotransmitter control or pharmacology of saccades [13]. It is known that visually-guided saccades are affected by drugs that alter arousal, including GABA receptor function, antihistamines and α2-adrenoceptor agonists and antagonists [14]. Based on the results of Smith and Nutt [11] it was predicted that noise would attenuate the reduction in saccade peak velocity following clonidine. The effects of the study drugs on cardiovascular parameters were recorded, both for safety purposes and to confirm that the doses administered were pharmacologically active. It was also of interest to determine whether the noise affected the cardiovascular system.

METHODS

Participants: Seventy-six males aged 18-35 years were recruited via advertisements and gave written informed consent to participate. All participants were evaluated by checking their medical history, giving them a physical examination and screening haematology and biochemistry tests. Participants who were taking medication, who were drinking more than 21 standard alcoholic drinks per week, or who had clinically relevant current or past illnesses, such as uncorrected visual disorders, hypertension or psychiatric disorders were excluded. Participants were instructed not to drink alcohol on the night

before the test. The study was approved by the medical ethics committee and conformed to the standards of the Declaration of Helsinki.

Design: A randomised, double-blind, between-participants group design was used, in which participants were divided into two groups to perform the post-treatment tests, either in quiet conditions or 80dB white noise, administered binaurally via headphones. Both of these groups were further randomized into four drug treatment groups: placebo; clonidine 200µg; idazoxan 40mg or the combination of clonidine 200µg and idazoxan 40mg, all administered orally. There were thus eight treatment groups with 9-10 participants per group. The drug doses were selected on the basis of showing effects on saccades and cardiovascular measures in previous studies [12]. All participants were well practised on the saccade task in a separate session prior to testing. On the test days participants arrived 30 minutes before the tests. Saccades were tested in four sessions at baseline and at an average of 45, 150 and 270 minutes post-drug. The timings were chosen to be in the absorption phase, around peak effects and around one half-life for the elimination of idazoxan. Between sessions participants did other psychomotor performance tasks and were allowed to move around when not performing tasks. A light lunch was given between the first and second post-drug sessions. All drugs were ingested orally at 11.00am, as two matched opaque capsules.

Saccade testing: The saccade test has been described previously [14]. Briefly, participants sat upright, with a headrest for support. They were instructed to follow a series of horizontal target movements on a light-emitting diode display. Eye movements were recorded by electrooculography and digitized at 512Hz, using the Cardiff Saccade Generating and Analysis System (CSGAAS 5, Cardiff University; [15]). After 4 saccades to settle into the task, a series of 24 saccades were completed, and the sequence repeated after a brief rest. Automated algorithms were used to identify components of saccades and to calculate the following parameters for individual saccades: peak velocity, accuracy (angle of saccade under- or overshoot of target angle) and latency (the interval between target movement and initiation of the saccade.

Heart rate and blood pressure: Heart rate and blood pressure were measured after 5 minutes rest from the saccade task without the headphones, using an automated sphygmomanometer.

Analysis: Five participants were excluded from the analysis: two due to inability to perform the saccade test adequately at baseline, two due to a technical problem with the saccade recording, and one due to a mild adverse reaction to idazoxan, with a tachycardia and light headedness. Due to baseline differences between some of the groups in saccade peak velocity and the cardiovascular parameters, these analyses were based on percentages of baseline values. Data were analysed using repeated measures analysis of variance, with grouping factors for drug and noise and a repeated time factor. The main interest of the study was in changes over time due to the drugs, noise or their interaction.

RESULTS

Saccadic eye movements: There were significant drug effects on peak velocity ($p < 0.001$) which was decreased by clonidine, compared with the other treatments, which did not differ from each other (Post hoc Student-Newman-Keuls tests : placebo = idazoxan + clonidine = idazoxan > clonidine). There was no change in saccade peak velocity over time in any of the groups apart from clonidine

(Table 1). There were no significant effects of drug on accuracy or peak velocity.Noise had no significant effects on saccade parameters, although saccade latency did decrease slightly in the noise condition (see Table 2).

Table 1: Drug effects on saccadic eye movement parameters at post-treatment sessions 1-3. Least square mean ± standard error of post-treatment values. Post-treatment values given as percent of baseline for peak velocity, acceleration, deceleration.

Post-drug session	**session 1**	**session 2**	**session 3**
Peak velocity			
placebo	104 ± 1.7	104 ± 1.6	104 ± 1.8
idazoxan 40mg + clonidine 200µg	101 ± 1.7	101 ± 1.6	101 ± 1.8
idazoxan 40mg	101 ± 1.7	101 ± 1.6	102 ± 1.8
clonidine 200µg	89 ± 1.7	88 ± 1.6	93 ± 1.8
Accuracy			
placebo	-1.2 ± 0.26	-0.9 ± 0.29	-1.0 ± 0.27
idazoxan 40mg + clonidine 200µg	-1.0 ± 0.26	-0.8 ± 0.29	-0.6 ± 0.27
idazoxan 40mg	-1.0 ± 0.27	-1.2 ± 0.30	-0.9 ± 0.27
clonidine 200µg	-1.2 ± 0.26	-1.1 ± 0.29	-0.9 ± 0.27
Latency			
placebo	172 ± 10.4	173 ± 10.2	173 ± 10.8
idazoxan 40mg + clonidine 200µg	174 ± 10.4	177 ± 10.2	168 ± 10.8
idazoxan 40mg	179 ± 10.6	183 ± 10.4	173 ± 11.0
clonidine 200µg	178 ± 10.4	176 ± 10.2	180±10.8

Table 2: 80dB noise effects on saccadic eye movement parameters at post-treatment sessions 1-3. Post-treatment values given as percent of baseline for peak velocity.

Post-drug session	**session 1**	**session 2**	**session 3**
Peak velocity			
noise	100 ± 1.2	98 ± 1.1	100 ± 1.3
quiet	98 ± 1.2	99 ± 1.2	99 ± 1.3
Latency (msec)			
noise	169 ± 7.2	176 ± 7.2	166 ± 7.5
quiet	182 ± 7.5	183 ± 7.4	181 ± 7.8

Cardiovascular responses: There were significant drug effects on blood pressure (systolic: $p < 0.001$; diastolic: $p < 0.001$) and heart rate ($p < 0.005$). Blood pressure was relatively stable in the placebo group, increased after idazoxan and decreased after clonidine (see Table 3). The effects with the combination of idazoxan and clonidine differed for systolic and diastolic blood pressure. Systolic pressure increased, although to a lesser extent than after idazoxan alone. Diastolic pressure changed little over the first two post-treatment sessions, but declined to 95% of baseline by the third session. At all points blood pressure was significantly higher in participants who received the combination of idazoxan and clonidine, than those who received clonidine alone. There were no significant interactions between time and noise. There was a trend for a time by noise effect for systolic blood pressure ($p = 0.08$), which increased somewhat to 103% of baseline in the noise condition, but this was only significant in the first post-drug session.

Table 3: Drug effects on cardiovascular parameters at post-treatment sessions 1-3. Least square mean ± standard error of post-treatment.

Post-drug session	**session 1**	**session 2**	**session 3**
Systolic BP			
Placebo	101 ± 2.3[a]	101 ± 1.9[a]	103 ± 1.9[b]
idazoxan 40mg + clonidine 200µg	108 ± 2.3	106 ± 1.9	102 ± 1.9
idazoxan 40mg	110 ± 2.4	109 ± 1.9	109 ± 2.0
clonidine 200µg	86 ± 2.3	84 ± 1.9	84 ± 1.9

Diastolic BP			
placebo	105 ± 1.9[b]	100 ± 1.9[c]	102 ± 2.0[d]
idazoxan 40mg + clonidine 200µg	101 ± 1.9	98 ± 1.9	95 ± 2.0
idazoxan 40mg	108 ± 2.0	106 ± 1.9	105 ± 2.1
clonidine 200µg	90 ± 1.9	83 ± 1.9	86 ± 2.0
Heart rate			
placebo	95 ± 2.8[e]	100 ± 2.8	98 ± 3.2
idazoxan 40mg + clonidine 200µg	93 ± 2.8	97 ± 2.8	93 ± 3.2
idazoxan 40mg	90 ± 2.9	97 ± 2.9	98 ± 3.3
clonidine 200µg	105 ± 2.8	100 ± 2.8	93 ± 3.2

DISCUSSION

This discussion starts with a summary of the effects of the drugs which were used to change noradrenergic functioning. This is then followed by a discussion of the effects of noise. Clonidine reduced saccade peak velocity, but did not alter saccade latency or accuracy, consistent with previous studies and other α_2-adrenoceptor agonists [16]. There was no decline in peak velocity over time in the placebo condition, which would be consistent with the idea that such declines may be related to relative behavioral inactivity, rather than fatigue as previously suggested. Saccade peak velocity was not increased by idazoxan alone, suggesting that if changes in noradrenergic neuronal firing and noradrenaline release modulate saccade velocity, this only occurs within a limited range, with the maximal effect already being achieved during normal active waking. The study confirmed the prediction that idazoxan would antagonize the saccade-slowing effect of clonidine, demonstrating that idazoxan 40mg produced significant and sustained antagonism of this central effect of clonidine.

Clonidine decreased and idazoxan increased blood pressure, consistent with previous human studies and with other α_2-adrenoceptor antagonists [17]. At the 40mg dose used, idazoxan fully blocked the hypotensive effect of clonidine 200µg. Although idazoxan antagonised the saccadic and hypotensive effects of clonidine, this is not in itself definitive evidence for mediation via α 2-adrenoceptors: clonidine also binds to α 1-adrenoceptors, 5HT1A receptors, imidazoline I1 sites and, with low affinity, I2 sites; idazoxan has greater α 2/α 1 selectivity than clonidine but has siimilar affinities at 5HT1A receptors and imidazoline I1 sites [18].

Noise did not modulate saccade parameters significantly, although there was a trend for a time by noise interaction for saccade latency, which tended to decrease slightly in the noise condition. The study therefore did not confirm the prediction that noise would activate the noradrenergic system and reverse the saccade slowing effect of clonidine. 80dB noise was reported previously to reduce attentional lapses following clonidine [11], so that the current data suggest that noise does not interact

with sustained attention and saccade control through a single mechanism, such an increase in noradrenergic neuron firing and norepinephrine release. It is possible that clonidine may exert additional postsynaptic effects at sites regulating saccades, that are not reversed by noise, or that the reversal of clonidine effects on sustained attention by noise was mediated via activation of other, for example dopaminergic or cholinergic, systems [19]. There was a trend effect for non-sustained effects of noise on systolic blood pressure, which agrees with earlier laboratory studies showing increases in blood pressure with noise, that were not always persistent after the termination of noise exposure [20].

There were several limitations of the current study. The electro-oculographic method is less sensitive for detecting small variations in saccade accuracy than methods that give a direct measure of eye position, such as infrared oculography [14]. Continuous white noise was used in the present study and other types of noise may produce different effects. For example, one recent study [21] has shown that sounds which deviate from a repeated sequence capture attention and can inhibit the programming of the next saccade.

In conclusion, idazoxan fully antagonized the effect of clonidine to slow saccade peak velocity, under test conditions in which it showed no intrinsic effects on this measure. The results did not show either main effects of noise or interactions with clonidine, which confirms the view that the effects of noise will depend on the nature of the task carried out [2, 3, 20].

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