Saccade dysfunction associated with chronic petrol sniffing and lead encephalopathy

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Background: In chronic petrol sniffers, recent exposure to high levels of leaded petrol may give rise to a lead encephalopathy characterised by tremor, chorea, ataxia, hyperreflexia, convulsive seizures, and death. Neurological abnormalities associated with lead encephalopathy involve the cortex, basal ganglia, cerebellum, and brain stem.

Objective: To use saccadic eye movement tasks as an experimental tool to determine which CNS changes are associated with chronic petrol sniffing and which with a history of lead encephalopathy, and to what extent these changes are reversible.

Methods: Saccade function was assessed in chronic petrol sniffers with a history of lead encephalopathy (encephalopathic sniffers), chronic petrol sniffers who had never suffered lead encephalopathy (chronic sniffers), individuals who had sniffed petrol in the past but had not done so for more than six months (ex-sniffers), and individuals who had never sniffed petrol (non-sniffers).

Results: Chronic sniffers showed increased latency of visually guided saccades and antisaccades and increased antisaccade errors which suggested cortical and basal ganglia dysfunction. These abnormalities returned to normal in ex-sniffers. Encephalopathic sniffers showed the same abnormalities as chronic sniffers but with greater severity and additional saccadic signs including dysmetria, gaze evoked nystagmus, and saccade slowing which usually indicate cerebellar and brain stem dysfunction.

Conclusions: Chronic petrol abuse is associated with cortical and basal ganglia abnormalities that are at least partially recoverable with abstinence. Additional long term cerebellar and brain stem abnormalities are associated with lead encephalopathy.

Abnormalities involving the cortex, basal ganglia, cerebellum, and brain stem.** These patients almost always have a long history of chronic recreational petrol abuse,*** so it is difficult to determine whether the neurological impairments and brain abnormalities are related to the chronic petrol sniffing, the lead encephalopathy, or both. In recreational petrol sniffers who had not suffered lead encephalopathy, we recently showed impairments in memory and attentional functions as well as neurological impairments that suggested abnormalities of the frontocerebellar brain regions.** However, the cognitive and neurological tasks were unable to dissociate performance measures that suggested cortical impairment from those arising from cerebellar or brain stem dysfunction.

Because saccades can be controlled, recorded, and quantified with much greater precision than most other interactive physiological variables, they have proven to be an excellent tool for detecting early and subtle changes in brain function related to neurodegenerative or neuropsychiatric disease. Different classes of saccade eye movements can be distinguished, each of which has a certain function and a distinct anatomical substrate and physiological organisation.** To determine the extent of saccade abnormalities that may be associated with chronic petrol sniffing or lead encephalopathy, we assessed groups of chronic recreational petrol sniffers with and without a history of hospital admission for lead encephalopathy on a battery of saccadic function tests. To investigate whether any abnormal saccadic functions normalise with abstinence from petrol sniffing, we also studied individuals who had been chronic petrol sniffers in the past but had since abstained.

METHODS

Participants

The study was set in two remote Aboriginal communities in Arnhem Land in northern Australia, where petrol sniffing had been prevalent for many years. From these communities, 112 male volunteers agreed to participate in a prospective research trial to investigate health and social outcomes of petrol abuse.** We present data on a subgroup of 96 subjects (age range, 13 to 35 years) for whom saccade assessments were obtained at baseline. Participants were classified into groups according to their history of petrol sniffing, using the consensual methodology used in our earlier studies involving the same participants.** (see Clough et al**).

Participants who had never sniffed petrol were classified as non-sniffers or controls.
Participants who had sniffed petrol in the past for at least six months but, at the time of the study, had not sniffed petrol for the last six months were classified as ex-sniffers. On average, ex-sniffers had abstained from sniffing petrol for 2.6 (SD 3.3) years.

Participants who were currently and actively sniffing petrol and had done so for a period of at least six months were classified as chronic sniffers. No participant from the ex-sniffer or chronic sniffer groups had ever been admitted to hospital for lead encephalopathy from sniffing petrol.

Chronic sniffers who were currently living in the community but who had been admitted to hospital previously for lead encephalopathy from petrol sniffing were classified as encephalopathic sniffers. These individuals had required emergency hospital admission and ongoing intensive care treatment for lead encephalopathy on a median of 1.0 previous occasions (range one to six), confirmed by records at the Royal Darwin Hospital (RDH). Before testing for this study, the most recent admission for lead encephalopathy among these individuals was a median of 3.5 (range 1 to 7) years earlier, when they were admitted for a median of 25 days (5 to 118) and had a median blood lead of 4.6 µmol/l (1.69 to 7.25) on admission. Blood lead concentrations higher than 0.48 µmol/l are above Australian recommended safe limits, and concentrations above 3.85 µmol/l indicate lead poisoning.16 All of the encephalopathic sniffers, chronic sniffers, and ex-sniffers (using a retrospective rating) met the criteria for inhalant abuse from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.15 These individuals had inhaled a combination of leaded and unleaded petrol.

Study exclusion criteria included a history of head injury with loss of consciousness, known epilepsy, dependence on or abuse of alcohol or cannabis, and psychiatric disorders other than petrol abuse. Participants who had been sniffing petrol for less than 12 hours before testing were also excluded.

The final study sample consisted of 34 non-sniffers, 24 ex-sniffers, 22 chronic sniffers, and 16 encephalopathic sniffers.

**Procedures**

Ethical approval for the project was obtained from the institutional ethics committees, an independent Aboriginal ethics committee, and the town councils from the communities involved. Informed written consent was given by all participants before testing. Blood samples were taken from each participant and analysed to determine the concentration of lead and the hydrocarbons toluene and benzene.19 A standardised neurological examination was done by a physician, based on the ataxia staging and scoring system.17 This system rated ataxia and pyramidal and deep tendon reflexes. The physician who did the examination was blind to each participants’ petrol sniffing classification.

Eye movement (saccade) recordings were undertaken in a darkened room with the head stabilised, using a high resolution infrared scleral reflectance technique (IRIS, Skalar; bandwidth, dc to 100 Hz (−3 dB)). Participants were seated one metre from a horizontal display of light emitting diode (LED; 16.9 cd/m²; rise time 3 µs) visual targets, with computer controlled illumination timing. Eye and target position signals were digitised at 1 kHz and scored for off-line computer analysis. Eye velocity was calculated as the first differential of eye position with respect to time. The saccade tasks used in this study have been described in detail previously.18 Briefly, participants performed visually guided saccades to fixate random targets. Saccade latency was calculated as the time from the onset of the target to the onset of the saccade. A velocity detection threshold of ±20°/s was used to define the saccade onset and saccade end.

Saccade accuracy (gain) was calculated as the displacement of the final eye position with respect to the target position. The percentage of hypometric saccades (<85% of target), hypermetric saccades (>15% of target), and anticipatory saccades (<70 ms from target onset) was calculated for each participant. Duration and peak velocity for visually guided saccades were plotted against saccade amplitude.

Saccade recordings were examined by visual inspection for the following abnormalities: post-saccadic drift reflecting pulse–step mismatch; saccadic intrusions that are inappropriate saccades taking the eye away from the target during attempted fixation; and gaze evoked nystagmus, which shows difficulty maintaining eccentric fixation of the target (±10° and ±15°) characterised by an alternation between slow drift and corrective quick movements of the eye.20 For the antisaccade task, a central fixation point was offset simultaneously with the onset of a peripheral target. A correct antisaccade was a deliberate eye movement to the location in the opposite visual field of the target and equidistant from the centre. Any initial reflexive eye movement towards the target was scored as an error, even if a subsequent correction to the opposite side was made. The latency for the onset of correct antisaccades was recorded and a percentage error calculated.

**Data analysis**

Before analysis, the distributions of data for each performance measure were inspected for normality and heterogeneity of variance. Demographic, behavioural, and biochemical indices of petrol abuse, neurological, and saccade variables were compared between groups using analysis of variance (ANOVA), with post-hoc comparison between each of the petrol sniffer groups and the non-sniffer group using Dunnett’s test. Where no control data were available—such as for measures of the age when sniffing began, the volume of petrol sniffed each week, or the number of years spent sniffing petrol—data for each of the ex-sniffer and encephalopathic sniffer groups were compared with those of the chronic sniffer group. Where data were not normally distributed or were categorical, comparisons were done using Mann–Whitney U non-parametric analysis or Fischer’s exact test. Previously, we computed a global neurological abnormality score for each individual by summing the number of abnormal neurological assessments using only those symptoms that were identified as being related to petrol sniffing (maximum score, 8). These symptoms were postural tremor, tandem gait, finger to nose movements (dominant and non-dominant hands), rapid alternating hand movements (dominant and non-dominant hands), deep reflexes, and palmer mental reflexes. This neurological abnormality score was recruited for the present study and used to represent neurological performance in comparison with saccade data.

The amplitude range for saccades across all participants was 0.3° to 40.9°. In this amplitude range, the saccade duration–amplitude relation is best represented using a linear function,21 and the saccade peak velocity–amplitude relation is best represented using a square root function.22 From these functions, a duration gradient and a velocity coefficient were derived for each participant and used as the dependent variables representing saccade duration and saccade peak velocity for analysis between the groups. Dose–response relations were investigated using Pearson’s product–moment correlation between measures of the severity of petrol abuse (age started sniffing, volume petrol sniffed each week, number of years sniffing) and biochemical measures (blood lead and blood toluene concentrations) compared with the neurological abnormality score and performance on saccade tasks. The level of significance for comparisons within each of
the domains assessed (demographic, behavioural, biochemical, neurological, and saccade) was set at 0.05.

RESULTS

Demographic, behavioural, and biochemical measures

Demographic, behavioural, and biochemical data are given in table 1. For the ex-sniffer, chronic sniffer, and encephalopathic sniffer groups combined, the duration of sniffing in years correlated positively with blood lead level \((r = 0.472, p=0.001)\) and the volume of petrol sniffed per week \((r = 0.409, p=0.002)\), and negatively with the age petrol sniffing began \((r = -0.610, p<0.001)\). For the ex-sniffer group, the number of years of abstinence since petrol sniffing correlated negatively with blood lead concentration \((r = -0.475, p = 0.03)\). Blood hydrocarbon level did not correlate with any measure of petrol sniffing behaviour.

Neurological assessment

Group means, standard deviations, and statistical variables for each of the neurological and saccade measures are shown in table 2. In comparison with non-sniffers, the neurological abnormality score was increased in ex-sniffers, and increased to a greater extent in both chronic sniffers and encephalopathic sniffers.

Saccade assessment

Visually guided saccades

In comparison with non-sniffers, ex-sniffers showed no saccadic abnormalities. Compared with non-sniffers, chronic sniffers had a significant increase in saccade latency but no further abnormalities for visually guided saccades. Compared with non-sniffers, the performance of encephalopathic sniffers on the visually guided saccade task was characterised by increased rates of saccadic intrusions, post-saccadic drift, gaze evoked nystagmus, hypometric and hypermetric saccades, anticipatory saccades, increased saccade latency, and reduced peak velocity.

Antisaccades

Performance of ex-sniffers was the same as for non-sniffers. Antisaccade error rate was increased significantly in both the chronic sniffer and encephalopathic sniffer groups compared with the non-sniffer group. Compared with non-sniffers, antisaccade latency was also increased in the chronic sniffer group and to a greater extent in the encephalopathic sniffer group.

Relations between petrol sniffing severity and biochemical measures and neurological and saccadic measures

Age was not correlated with any measure of neurological or saccadic performance for all four groups combined. For the ex-sniffer group, the number of years of abstinence from petrol sniffing correlated negatively with the percentage of hypometric saccades \((r = -0.44, p = 0.04)\) and positively with saccade accuracy \((r = 0.473, p = 0.03)\). For the encephalopathic sniffer group, the number of years since the most recent hospital admission for lead encephalopathy did not correlate with the neurological abnormality score or any saccade measure. Combining data for the ex-sniffer, chronic sniffer, and encephalopathic sniffer groups, the length of time petrol sniffing correlated positively with the neurological abnormality score \((r = 0.44; p<0.01)\), the percentage of hypometric saccades \((r = 0.37; p<0.01)\), saccade latency \((r = 0.33; p<0.05)\), antipsaccade latency \((r = 0.43; p<0.01)\), and antisaccade error rate \((r = 0.30; p<0.05)\), and negatively with saccade accuracy \((r = -0.32; p<0.05)\). Blood lead correlated positively with the neurological abnormality score \((r = 0.58; p<0.001)\) and antipsaccade latency \((r = 0.51; p<0.001)\). Blood toluene \((r = 0.67; p<0.001)\) and blood benzene \((r = 0.63; p<0.01)\) correlated with the proportion of hypermetric saccades but with no other neurological or saccade variables.

DISCUSSION

These data showed that chronic petrol sniffing is associated with raised blood lead and hydrocarbon levels, and with neurological and saccade impairments consistent with dysfunction of cortical and basal ganglia brain regions. These are at least partially recoverable with abstinence. Importantly, chronic petrol sniffers with a history of lead encephalopathy from petrol sniffing (hereafter called encephalopathic sniffers) showed additional saccade impairments that suggested cerebellar and brainstem abnormalities. Their saccadic abnormalities were characterised by increased saccadic and antipsaccade latency, increased antipsaccade error rates, saccadic intrusions, post-saccadic drift, gaze evoked nystagmus, increased anticipations, dysmetria, and a reduction in the peak velocity of visually guided saccades. For encephalopathic sniffers, strong evidence for a petrol related disruption to cerebellar and brainstem ocular motor areas was suggested by the dysmetria, gaze evoked nystagmus, and saccadic slowing. For example, a strong association between cerebellar abnormalities and saccadic dysmetria is shown in studies of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Paired comparisons between each of the ex-sniffer, chronic sniffer, and encephalopathic sniffer groups and the non-sniffer group for demographic, behavioural, and biochemical data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-sniffer (n = 34)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.0 (4.0)</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>14 to 32</td>
</tr>
<tr>
<td>Age petrol sniffing began (years)</td>
<td>–</td>
</tr>
<tr>
<td>Volume/week (No of 3/3 ml cans)</td>
<td>–</td>
</tr>
<tr>
<td>Duration sniffing (years)</td>
<td>–</td>
</tr>
<tr>
<td>Blood lead (µmol/l)</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>Detectible toluene (%)</td>
<td>0</td>
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<tr>
<td>Blood toluene (µmol/l)</td>
<td>–</td>
</tr>
<tr>
<td>Detectible benzene (%)</td>
<td>0</td>
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<tr>
<td>Blood benzene (µmol/l)</td>
<td>–</td>
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</tbody>
</table>

Unless otherwise stated, data are presented as group mean (SD).

*p<0.05; **p<0.01; ***p<0.001; comparisons made between non-sniffer group and all other groups, except variables flagged with superscript a, where comparisons are with the chronic sniffer group.
Saccade effects of petrol sniffing

humans with degenerative cerebellar disorders and generalised cerebellar brain lesions in both primates and humans. Individuals with cerebellar abnormalities also show gaze evoked nystagmus and saccadic slowing is commonly reported in individuals with lesions affecting both cerebellar and pontine brain regions.

Chronic petrol sniffers with no history of hospital admission for lead encephalopathy (hereafter called non-encephalopathic sniffers) began sniffing petrol at the same age and had sniffed for the same number of years as the encephalopathic sniffers. However, in comparison with the encephalopathic sniffers, they had a lower exposure to petrol as they had abstained for longer than six months showed mild neurological abnormalities and no saccadic abnormalities. This reduction in the extent and severity of neurobehavioural impairment with abstinence from petrol sniffing is consistent with our previous cognitive data that showed only subtle memory and attentional dysfunction in ex-sniffers. These data suggest that at least some of the neurological deficits associated with recreational petrol abuse may be ameliorated by abstinence. Importantly, none of the ex-sniffers had a history of lead encephalopathy from petrol sniffing and all the participants from our study who had been admitted to hospital with lead encephalopathy continued to sniff petrol upon discharge. Consequently, we were not able to determine the nature or magnitude of improvement in neurological and saccade function that is possible with abstinence from petrol sniffing after lead encephalopathy has occurred.

These results showed that blood lead and blood hydrocarbon levels, as well as the length of time spent petrol sniffing, correlated with the magnitude of neurological and saccade impairment. As in our previous study, this suggested that the extent of brain dysfunction among petrol sniffers is determined by the severity of their past exposure to petrol. Many studies have reported positive relations between blood lead levels and cognitive performance. When inhaled, lead is stored by bone and fat for many years and slowly released into the circulation; consequently there is a continued decline of cognitive function for up to 16 years after the most recent exposure to lead. Thus, although leaded petrol has not been available in Australia since 2002, past exposure may continue to have a detrimental impact on brain function even years after petrol sniffing has stopped.

The neurological and saccade impairments observed here in petrol sniffers are qualitatively similar to those found in chronic sniffers of hydrocarbon solvents. However, whereas those inhalant abusers were exposed only to hydrocarbons, the current group of petrol sniffers had abused both leaded and unleaded varieties of petrol, and were

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| Table 2 | Paired comparisons between each of the ex-sniffer, chronic sniffer, and encephalopathic sniffer groups and the non-sniffer group for neurological and saccade data |
|---|---|---|---|---|---|
| **Non-sniffer (n = 34)** | **Ex-sniffer (n = 24)** | **Chronic sniffer (n = 22)** | **Encephalopathic sniffer (n = 16)** | **F statistic** |
| **Neurological abnormality score (max = 8)** | 0.5 (1.1) | 1.3 (1.5)* | 3.1 (1.8)** | 5.9 (2.6)** | 42.4 |
| **Visually guided saccades** | | | | | |
| Saccadic intrusions† | 10 | 4 | 9 | 12** |
| Post-saccadic drift‡ | 4 | 4 | 2 | 12** |
| Gaze evoked nystagmus | 0 | 1 | 0 | 0 |
| Hypometric (%) | 19.4 (5 to 53) | 22.3 (4 to 59) | 23.2 (2 to 67) | 29.5 (4 to 70)* | 1.5 |
| Hypometric (%) | 7.7 (0 to 28) | 7.0 (0 to 35) | 6.3 (0 to 18) | 14.0 (0 to 47)* | 2.8 |
| Anticipations (%) | 10.0 (0 to 47) | 8.5 (0 to 51) | 13.2 (0 to 42) | 18.6 (3 to 74)* | 2.4 |
| Latency (ms) | 170.2 (22.7) | 175.5 (25.2) | 158.2 (27.2) | 205.3 (32.1)** | 7.0 |
| Accuracy (%) | 98.8 (12.6) | 92.2 (6.6) | 94.3 (7.0) | 93.8 (11.8) | 1.3 |
| Peak velocity§ | 133.7 (20.5) | 131.7 (19.1) | 129.3 (23.6) | 119.4 (23.6)* | 1.7 |
| For 10° saccades (°/s) | 432 | 416 | 409 | 378 |
| For 20° saccades (°/s) | 598 | 589 | 578 | 534 |
| Duration¶ | 2.2 (0.5) | 2.2 (0.7) | 2.3 (0.8) | 2.4 (0.6) | 1.0 |
| Antisaccades | 39 | 39 | 40 | 41 |
| Latency (ms) | 261.4 (38.4) | 280.3 (65.0) | 300.8 (62.8)** | 406.1 (99.2)** | 15.4 |
| Error rate (%) | 16.3 (12.0) | 26.0 (27.4) | 40.7 (53.6)** | 52.3 (37.4)** | 7.1 |

Values are median (range) or mean (SD).

†Scored as the number of participants from each group who show these saccade characteristics.

‡To give meaningful examples of the data, measures of peak velocity and saccade duration were derived from the coefficient and gradient scores, respectively, for saccade amplitudes of 10° and 20°.

* p<0.05; ** p<0.01; *** p<0.001; comparisons made between the non-sniffer group and all other groups.

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therefore inhaling organic lead as well as the hydrocarbons toluene, xylene, and benzene. These data suggest that the toxicity of both lead and hydrocarbons contributes to the decline in neurobehavioural function that occurs in petrol sniffers, although the specific toxic effects of each of these chemicals could not be isolated.

The abuse of petrol and other inhalants is often prevalent among indigenous groups who have limited English language skills, limited experience with cognitive or neurological testing, and live in remote isolated areas where there is no access to modern medical technologies such as brain imaging. In addition, given the recent finding that neuropsychological tests were not a good indicator of brain abnormalities among solvent abusers, saccade testing provides an ideal culturally appropriate assessment tool that is suitable for use in remote indigenous communities and which has proven validity for the early detection of neurological degeneration.

**REFERENCES**