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Neurological and Cognitive Recovery Following Abstinence from Petrol Sniffing

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Anecdotal observations suggest that neurological impairments associated with petrol (gasoline) sniffing resolve with abstinence, although these effects have not been proven empirically. Severe exposure to leaded petrol may induce a lead encephalopathy that extends beyond any acute intoxication and requires emergency hospital treatment. Previously, in chronic petrol sniffers, we showed neurological, saccadic, and cognitive abnormalities that were more severe in petrol sniffers with a history of hospitalization for lead encephalopathy, and that correlated with blood lead levels and the length of time of sniffing petrol. Ex-petrol sniffers showed a qualitatively similar but quantitatively less severe pattern of impairment. Petrol sniffing was stopped completely in one of the study communities by modifying social, occupational, and recreational opportunities. After 2 years, we obtained biochemical and neurobehavioral (neurological, saccade, and cognitive) data from all available participants of the earlier study including 10 nonsniffers and 29 chronic petrol sniffers, with six of these individuals previously receiving hospital treatment for lead encephalopathy. Here, we report that blood lead was reduced and that neurobehavioral impairments improved, and in many cases normalized completely. The most severe petrol-related neurobehavioral impairment was observed among individuals who had longer histories of abuse and higher blood lead levels, and among petrol sniffers with a history of lead encephalopathy. Those with the greatest extent of neurobehavioral impairment showed the greatest degree of improvement with abstinence, but were less likely to recover completely. This is the first direct evidence that neurological and cognitive impairment from chronic petrol sniffing ameliorates with abstinence and may recover completely.
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INTRODUCTION

Although there is no direct evidence, the cognitive and neurological effects of petrol (gasoline) inhalation (aka petrol sniffing, huffing) are considered to resolve when individuals abstain from abuse. This is because individuals who abstain from abusing other inhalants that also contain volatile hydrocarbons (ie, glue, lighter fluid) show improvement in neurological function and cognitive performance (Brust, 1993; Sharp and Rosenberg, 1996). In addition, case reports of severely impaired petrol sniffers treated with chelation therapy show that brain changes associated with petrol abuse recover when individuals abstain from further sniffing (Goldings and Stewart, 1982; Kurt *et al*, 1982; Brown, 1983; Fortenberry, 1985; Currie *et al*, 1994). Finally, cross-sectional studies comparing active- and ex-petrol sniffers show that cognitive and neurological abnormalities in ex-sniffers are qualitatively similar but quantitatively less severe than those in active sniffers matched for age and history of abuse (Maruff *et al*, 1998; Cairney *et al*, 2004a, b). However, there have been no prospective studies of the abstinence from petrol sniffing on central nervous system (CNS) function.

Petrol contains neurotoxic substances including aromatic hydrocarbons and tetraethyl lead that, when inhaled, induce euphoria, relaxation, diplopia, slurred speech, and hallucinations (Brust, 1993; Cairney *et al*, 2002). Severe exposure to leaded petrol may induce a lead encephalopathy that extends beyond the period of acute intoxication and is characterized by a 'clouding' of conscious state, tremor, myoclonus or chorea, limb and gait ataxia, hyperreflexia, nystagmus, and convulsive seizures. In some cases death may occur (Goldings and Stewart, 1982; Coulehan *et al*, 1983; Cairney *et al*, 2002). Consequently, individuals with lead encephalopathy secondary to petrol abuse require emergency hospitalization that is usually followed by prolonged intensive care treatment (Currie *et al*, 1994;

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Goodheart and Dunne, 1994). Studies of petrol sniffers who have recovered from lead encephalopathy and been discharged from hospital show that while the acute symptoms eventually subside, considerable neurological and cognitive impairments remain (Cairney *et al*, 2004a, b). These include gait ataxia, dysdiadochokinesia, postural tremor, positive palmomental reflexes, brisk deep reflexes, saccadic slowing, nystagmus, dysmetria, increased saccadic latencies, saccadic disinhibition, impaired visual attention, visual recognition memory, and visual paired associate learning.

Recreational petrol sniffers who have not suffered lead encephalopathy show similar impairments in cognitive and neurological function, but reduced in magnitude compared with those observed in community dwelling individuals who are recovering from lead encephalopathy (Maruff *et al*, 1998; Cairney *et al*, 2004a). This indicates that CNS changes do occur with relatively mild exposure to petrol sniffing. Interestingly though, nonencephalopathic petrol sniffers do not show any saccadic slowing, dysmetria, or nystagmus suggesting that additional CNS areas are disrupted by lead encephalopathy. Saccadic slowing, dysmetria, and nystagmus are all hallmarks of cerebellar damage (Bötzel *et al*, 1993; Moschner *et al*, 1994; Wessel *et al*, 1998), suggesting that this area is specifically sensitive to lead encephalopathy, a hypothesis consistent with the clinical and case reports of movement abnormalities in individuals admitted to emergency rooms after petrol sniffing. Individuals who have been petrol sniffers in the past but have abstained for more than 6 months and have not suffered lead encephalopathy also show neurological and cognitive impairment, although this is very mild compared to active petrol sniffers (Maruff *et al*, 1998; Cairney *et al*, 2004a). When considered together these cross-sectional data suggest that there is recovery from petrol-related CNS dysfunction. However, the nature of recovery may depend on the severity of abuse and whether or not there was lead encephalopathy. In addition, these data do not indicate whether such improvement continues until cognitive and neurological functions are restored completely. Therefore, prospective studies are required to confirm that CNS improvement occurs with abstinence from petrol sniffing and to determine the nature and magnitude of this improvement.

In one of the remote regions where we have studied petrol sniffing, a community intervention successfully eradicated the practice of petrol sniffing through the replacement of petrol with Aviation gasoline (Avgas) in the fuel supply and the implementation of employment and skills training programs (Burns *et al*, 1995a). Prior to the intervention, baseline data were collected on a range of social, biochemical, and neurobehavioral indices (Burns *et al*, 1995b; Maruff *et al*, 1998; Cairney *et al*, 2004a, b). Following the intervention, crime rates were reduced significantly and employment increased among individuals who had stopped sniffing petrol (Burns *et al*, 1995a). At 2 years after the intervention and the corresponding abolition of petrol sniffing, follow-up assessments of biochemical and neurobehavioral (neurological, saccade, and cognitive) function were obtained from all participants of the original study who remained in the community. Here we present neurological, saccade, and cognitive data obtained from petrol sniffers both with and without a history of lead encephalopathy at baseline, and following 2 years of abstinence from petrol sniffing.

METHODS

Participants

Ethical approval for the project was obtained from the institutional ethics committee, an independent Aboriginal ethics committee and the town councils from the communities involved. Informed written consent to participate was given by all participants prior to testing. Previously, we have published baseline data that was collected from a total of 112 male participants from two remote Aboriginal communities in Arnhem Land in northern Australia (Burns *et al*, 1995a, b; Maruff *et al*, 1998; Cairney *et al*, 2004a, b). In one of these communities, an intervention successfully eradicated the practice of petrol through the replacement of petrol with Aviation gas (Avgas) and the implementation of employment and social programs. The intervention has been described in detail previously and verification provided of its success in eliminating petrol sniffing (Burns *et al*, 1995a). From this community, baseline data had been collected from 55 males aged 13–32 years (mean age = 21 years, SD = 5 years), who were classified as either nonsniffers who had never sniffed petrol ($n = 13$), ex-sniffers who had sniffed petrol in the past for at least 6 months but who had since abstained for at least 6 months at the time of testing ($n = 15$), and current sniffers who were currently and actively sniffing petrol ($n = 27$; Burns *et al*, 1995a). These individuals represented 29% of the total male population in this age group living in the community (total = 188). Data presented in the current study were collected 2 years after this intervention and the corresponding abolition of petrol sniffing. We were able to obtain follow-up biochemical (blood lead) and neurobehavioral (neurological, saccade, and cognitive) assessments for 39 of the original participants. Of these, 10 were nonsniffers and 29 had been chronic petrol sniffers prior to the intervention, with only six having had a previous history of hospitalization for lead encephalopathy from the severe abuse of leaded petrol. As described previously (Cairney *et al*, 2004a, b), the criteria for defining lead encephalopathy were emergency evacuation to the nearest regional hospital that required admission to the intensive care unit and, on admission, the presentation of typical clinical signs including confusion, drowsiness, aggression, hallucinations, ataxia, intention tremor, nystagmus, and grand mal seizure. Hospital admissions were confirmed by records at Royal Darwin Hospital (RDH). Our baseline data showed a greater extent of neurobehavioral impairment among petrol sniffers with a history of lead encephalopathy arising from petrol sniffing (Cairney *et al*, 2004a, b), and these individuals were therefore treated as a different group and analyzed separately. Chronic petrol sniffers with no history of hospitalization for lead encephalopathy are referred to as nonencephalopathic sniffers ($n = 23$) and chronic petrol sniffers with a history of hospitalization with lead encephalopathy arising from petrol sniffing are referred to as encephalopathic-sniffers ($n = 6$). Follow-up data were not obtained from 16 of the original participants, 13 of whom were absent from the community including one individual

who was reportedly sniffing petrol elsewhere. Arnhem Land communities comprise an integration of clan and family groups, whose associations and activities are well-known throughout the community. Consequently, Aboriginal health workers usually have a detailed knowledge about individual practices from within their community, including those related to substance abuse. Aboriginal health workers verified that, at the time of testing which took place in the community, no participant had sniffed petrol since the intervention 2 years earlier. At baseline, all of the petrol sniffers met the criteria for inhalant abuse from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994) and had inhaled a combination of leaded and unleaded petrol. Exclusion criteria was the same as at baseline (Maruff *et al*, 1998; Cairney *et al*, 2004a, b), and included a history of known epilepsy, dependence or abuse of alcohol or cannabis and psychiatric disorder other than petrol abuse.

Procedure

The same methods that were used to collect and analyze the baseline data were also used here for the follow-up, and these have been described in detail previously (Burns *et al*, 1994a; Maruff *et al*, 1998; Cairney *et al*, 2004a, b). In brief, group classifications were verified according to the consensual methodology that required corroborating information from the participant, local community health workers, paid indigenous research assistants from the same clan, and local health records (Burns *et al*, 1995a, b; Maruff *et al*, 1998; Clough *et al*, 2002; Cairney *et al*, 2003). Blood samples were taken from each participant and analyzed to determine the concentration of lead. A standardized neurological examination was administered by a physician, on the basis of the Ataxia Staging and Scoring System (Pourcher and Barbeau, 1980). The physician who performed the examination was blind to each participants' history of petrol sniffing. Eye movement (saccade) recordings were performed in a darkened room with the head stabilized, using a high-resolution infrared scleral reflectance technique (IRIS, Skalar; band width DC to 100 Hz (−3 dB)). Participants were seated 1 m from a horizontal display of light-emitting diode (LED; 16.9 cd/m^2; rise time 3 μs) visual targets with computer controlled illumination timing. Eye and target position signals were digitized at 1 kHz and scored for offline computer analysis. Eye position was differentiated using a computer-based algorithm to obtain eye velocity. The saccade tasks used in this study have been described in detail previously (Currie *et al*, 1992; Cairney *et al*, 2003). Briefly, participants performed visually guided saccades to fixate random targets. Saccade latency was calculated as the duration from the onset of the target to the onset of the saccade. Antisaccades were volitional saccades, made from a central fixation point that is offset simultaneously with the onset of a peripheral target, to the mirror location of the peripheral target. 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. The cognitive test battery was drawn from the touchscreen based Cambridge Automated Neuropsychological Test Battery (CANTAB) that included tests of basic movement reaction time (simple reaction time task), visual recognition memory (pattern recognition task), visual attention (visual search task), and visuo-spatial learning/memory (pattern-location paired associative learning task). Methods for the use of these tests in indigenous groups have been described in detail previously (Maruff *et al*, 1996, 1998; Cairney *et al*, 2003).

Data Analysis

Before analysis, the distributions of data for each performance measure were inspected for normality and heterogeneity of variance. Raw data that were positively skewed were normalized using logarithmic base 10 (log) transformation and negatively skewed data were normalized using arcsine transformations (eg, Maruff *et al*, 1996, 1998). Individual data for age, blood lead level, saccade, and cognitive indices were compared with a 2 (time: baseline, follow-up) × 3 (group: controls, nonencephalopathic sniffers, encephalopathic sniffers) analyses of variance (ANOVA). Where there were significant interactions, group differences were investigated using LSD *post hoc* *t*-test comparisons. Paired samples *t*-tests were used to compare performances for each group between baseline and follow-up. Neurological measures were compared between groups and between baseline and follow-up using χ^2 tests or Fisher's exact test for nonparametric data. Using the measures where petrol sniffers showed improvement with abstinence (dysdiadochokinesia, deep tendon reflexes, palmomental reflexes, postural tremor, antisaccade errors, paired associate learning accuracy, pattern recognition accuracy, and visual search accuracy), individual scores were rated as either normal or abnormal. At baseline and follow-up, a global abnormality score was then calculated for each participant as the sum of abnormal assessments (maximum = 8). Global abnormality scores were compared between groups using Kruskal–Wallis tests and between baseline and follow-up using the Wilcoxon Signed Ranks test. Participants were considered to have general neurobehavioral impairment if this global abnormality score was above normal limits (>3). For blood lead levels, saccade, cognitive measures, and the global abnormality score, abnormal performance scores were identified based on 99% confidence intervals calculated from control data. For each participant, the magnitude of improvement was calculated as the difference in the global abnormality score between baseline and follow-up. Relationships between the number of years of petrol sniffing or blood lead levels and neurobehavioral measures including the global abnormality score (baseline and follow-up) and the magnitude of improvement were investigated using Spearman's coefficient for nonparametric data and Pearson's product moment correlation for parametric data. The level of significance for comparisons within each of the domains assessed was set at 0.05.

RESULTS

Table 1 shows group mean scores and comparisons for age, number of years sniffing, and blood lead level. Mean scores

Table 1 Comparisons between Nonsniffers, NE-Sniffers, and E-Sniffers at Baseline and Follow-up (+2 years) for Age, Number of Years Sniffing and Blood Lead Level

	Nonsniffers ($n=10$)	NE-sniffers ($n=23$)	E-sniffers ($n=6$)	Statistic	*p*-value
Age (mean)	18.1	21.0	27.2[a]	$F=8.6$	0.01
Age range	(13–29)	(14–29)	(21–32)		
No. years sniffing		7.7 (4.7)	13.0 (5.6)[a]	$t=-2.2$	0.04
Blood lead level (μM/l)					
Baseline	0.3 (0.2)	1.4 (0.6)[b]	2.5 (0.6)[a,b]	$F=33.1$	<0.001
+2 years	0.3 (0.1)	**0.9** (0.4)[b]	**1.4** (0.6)[a,b]	$F=16.4$	<0.001

Unless otherwise stated, all data presented as mean (SD).
Bold print indicates improved score from baseline to follow-up (+2 years).
[a]Signficant difference between E-sniffers and NE-sniffers scores.
[b]Signficant difference with control scores.
All indicated changes tested at $p<0.05$.

and comparisons for neurological, saccade, and cognitive data are shown in Table 2. Repeated measures 2 (time: baseline, follow-up) × 3 (group: controls, NE-sniffers, E-sniffers) ANOVAs showed significant group interactions for blood lead levels ($F=13.86$; $p<0.001$, $\eta^2=0.44$), antisaccade errors ($F=6.03$; $p=0.006$; $\eta^2=0.27$), and paired associate learning accuracy ($F=7.00$; $p=0.003$; $\eta^2=0.28$). Using age and blood lead level at baseline as covariates did not affect these interactions, which remained significant for antisaccade errors ($F=3.31$; $p=0.05$; $\eta^2=0.18$) and paired associate learning accuracy ($F=5.39$; $p=0.009$; $\eta^2=0.25$).

At baseline, there was a significant group effect for blood lead level ($F=33.05$; $p<0.001$; $\eta^2=0.65$), tandem gait ($\chi^2=12.23$; $p<0.01$), dysdiadochokinesia ($\chi^2=8.53$; $p<0.025$), deep tendon reflexes ($\chi^2=16.41$; $p<0.001$), palmomental reflex ($\chi^2=7.27$; $p<0.05$), postural tremor ($\chi^2=15.33$; $p<0.001$), antisaccade errors ($F=7.26$; $p=0.002$; $\eta^2=0.31$), paired associate learning ($F=17.27$; $p<0.001$; $\eta^2=0.49$), visual search with eight shapes ($F=4.86$; $p=0.01$; $\eta^2=0.21$), pattern recognition performance ($F=11.93$; $p<0.001$; $\eta^2=0.40$), and the global abnormality score ($\chi^2=22.43$; $p<0.001$). After 2 years, significant group effects remained for all of the neurological tasks including tandem gait ($\chi^2=12.98$; $p<0.01$), dysdiadochokinesia ($\chi^2=6.38$; $p<0.05$), deep tendon reflexes ($\chi^2=14.54$; $p<0.001$), palmomental reflex ($\chi^2=7.44$; $p<0.025$), postural tremor ($\chi^2=9.24$; $p<0.01$) and for only two cognitive tasks. These were the paired associate learning task ($F=3.92$; $p=0.03$; $\eta^2=0.18$) and the pattern recognition task ($F=7.37$; $p=0.002$; $\eta^2=0.29$). A group effect for the global abnormality score also remained ($\chi^2=12.16$; $p=0.002$). Further analysis of these data showed that, compared to healthy controls at baseline, nonencephalopathic sniffers showed elevated blood lead ($p<0.001$), positive palmomental reflexes ($p=0.02$), postural tremor ($p<0.001$), increased errors on the antisaccade task ($p=0.03$), the paired associate learning task ($p<0.001$), the visual search task (with 8 shapes; $p=0.01$), the pattern recognition task ($p<0.001$), and a greater global abnormality score ($p<0.001$). Following 2 years of abstinence from petrol sniffing, blood lead ($p<0.001$) and performance on the pattern recognition memory task remained abnormal ($p=0.002$) and the global abnormality score was significantly greater ($p=0.01$), whereas all other impairments were normalized. Compared to healthy controls at baseline, encephalopathic sniffers showed elevated blood lead ($p<0.001$), abnormal tandem gait ($p=0.001$), rapid alternating hand movements (dysdiadochokinesia; $p=0.008$), and deep tendon reflexes ($p=0.001$), positive palmomental reflexes ($p=0.04$), postural tremor ($p=0.03$), increased errors on the antisaccade task ($p=0.001$) as well as the paired associate learning task ($p<0.001$), the visual search task (with eight shapes; $p=0.009$) and the pattern recognition task ($p<0.001$), and also showed a greater global abnormality score ($p<0.001$). Following 2 years of abstinence from petrol sniffing, blood lead ($p<0.001$), tandem gait ($p=0.001$), dysdiadochokinesia ($p=0.04$), deep tendon reflexes ($p=0.008$), palmomental reflexes ($p=0.04$), postural tremor ($p=0.04$), and performance on the paired associate learning task ($p=0.008$), the pattern recognition memory task ($p=0.002$), and the global abnormality score ($p=0.002$) remained abnormal whereas all other impairments returned to normal.

Using paired samples comparisons between baseline and follow-up (+ 2 years), the control group showed no change in blood lead level and no change in any neurobehavioral measure. By contrast, nonencephalopathic sniffers showed a significant reduction in blood lead levels ($t(22)=6.07$; $p<0.001$) and improvements in palmomental reflex abnormalities ($\chi^2=9.58$; $p<0.01$), postural tremor ($\chi^2=8.17$; $p<0.01$), antisaccade errors ($t(20)=4.08$; $p=0.001$), paired associate learning errors ($t(22)=5.41$; $p<0.001$) and the global abnormality score ($Z=-3.95$; $p<0.001$). The nonencephalopathic group showed no significant changes in performance over time for any other measure. Encephalopathic sniffers also showed a significant reduction in blood lead levels ($t(5)=4.67$; $p=0.006$), antisaccade errors ($t(5)=2.97$; $p=0.03$), and an improvement in visual search accuracy with eight shapes ($t(5)=-2.78$; $p=0.04$) and

Table 2 Comparisons between Nonsniffers, NE-Sniffers and E-Sniffers at Baseline and Follow-up (+2 years) for Neurological, Saccade and Cognitive Data (NE = Nonencephalopathic; E = Encephalopathic)

Time	Nonsniffers ($n=10$)	NE-sniffers ($n=23$)	E-sniffers ($n=6$)	*p*-value
Tandem gait (number abnormal)				
0	0 (0%)	7 (30%)	5 (83%)[a]	<0.01
+2 y	0 (0%)	6 (26%)	5 (83%)[a,b]	<0.01
Dysdiadochokinesia (number abnormal)				
0	1 (10%)	9 (39%)	5 (83%)[a]	<0.025
+2 y	0 (0%)	4 (17%)	3 (50%)[a]	<0.05
Deep tendon reflexes (number abnormal)				
0	1 (10%)	5 (22%)	6 (100%)[a,b]	<0.001
+2 y	1 (10%)	**3** (13%)	5 (83%)[a,b]	<0.001
Palmomental reflex (number abnormal)				
0	1 (10%)	13 (57%)[a]	4 (67%)[a]	<0.05
+2 y	0 (0%)	3 (13%)	3 (50%)[a]	<0.025
Postural tremor (number abnormal)				
0	2 (20%)	20 (87%)[a]	5 (83%)[a]	<0.001
+2 y	0 (0%)	**2** (9%)	3 (50%)[a,b]	<0.01
Saccade latency (ms)				
0	185.9 (20.3)	182.8 (29.9)	203.2 (28.8)	NS
+2 y	175.5 (17.6)	171.0 (29.3)	179.4 (26.2)	NS
Antisaccade latency (ms)				
0	273.0 (28.7)	305.9 (68.7)	351.0 (39.6)	NS
+2 y	277.3 (48.4)	283.9 (61.8)	309.3 (35.8)	NS
Antisaccade errors (%)				
0	16.4 (9.8)	46.5 (23.5)[a]	77.0 (36.1)[a,b]	0.003
+2 y	17.1 (14.6)	**23.5** (17.9)	**29.2** (16.5)	NS
Simple reaction time (log lat)				
0	2.9 (0.2)	2.9 (0.1)	2.9 (0.2)	NS
+2 y	2.8 (0.1)	2.8 (0.1)	2.8 (0.1)	NS
Paired associate learning (total errors)				
0	3.2 (2.3)	23.3 (13.0)[a]	33.0 (10.0)	<0.001
+2 y	5.3 (3.8)	**11.0** (11.2)	21.5 (18.2)[a,b]	0.03
Visual search two shapes (arcsine % accuracy)				
0	1.6 (0)	1.5 (0.04)	1.4 (0.1)	NS
+2 y	1.6 (0)	1.5 (0.1)	1.6 (0)	NS
Visual search eight shapes (arcsine % accuracy)				
0	1.5 (0.2)	1.2 (0.3)[a]	1.0 (0.4)[a]	0.01
+2 y	1.6 (0)	1.3 (0.5)	**1.5** (0.2)	NS
Pattern recognition (arcsine % accuracy)				
0	1.0 (0.2)	0.7 (0.2)[a]	0.6 (0.1)[a]	<0.001
+2 y	1.0 (0.2)	0.8 (0.2)[a]	0.7 (0.1)[a]	0.002
Global abnormality score				
0	1.00 (1.25)	4.35 (1.75)[a]	6.50 (1.05)[a,b]	<0.001
+2 y	0.40 (0.84)	**1.70** (1.64)[a]	**3.67** (2.34)[a,b]	0.002

Unless otherwise stated, all data presented as mean (SD). Bold print indicates improved score from baseline to follow-up (+2 years).
[a]Signficant difference with control scores.
[b]Signficant difference between E-sniffers and NE-sniffers scores.
All indicated changes tested at $p<0.05$.

global abnormality score ($Z=-2.23$; $p=0.03$). The encephalopathic group showed no significant changes in performance over time for any other measure. Figure 1 shows the percentage from each group who showed the neurological abnormalities of palmomental reflex (a) and postural tremor (b) at baseline and follow-up ($+2$ years). Figure 2 shows group mean scores for antisaccade percentage errors (a), total errors on the paired associate learning task (b), and visual search accuracy (c).

Effects of Lead Encephalopathy on Impairment, Improvement and Normalization

In comparison to nonencephalopathic sniffers, encephalopathic sniffers were older ($t=-3.4$; $p=0.002$), had sniffed petrol for more years ($t=-2.2$; $p=0.04$), showed higher blood lead levels ($t=-3.7$; $p=0.001$), and a greater abnormality score at both baseline ($t=-2.9$; $p=0.008$) and follow-up ($t=-2.4$; $p=0.02$), but no difference in the magnitude of improvement with abstinence ($t=-0.2$; $p=0.82$). The global abnormality score showed that 70% ($n=16$) of nonencephalopathic sniffers showed general neurobehavioral impairment at baseline and only 44% ($n=7$) of these individuals remained impaired at follow-up, and that 100% ($n=6$) of encephalopathic sniffers showed general neurobehavioral impairment at baseline and 83% ($n=5$) of these individuals remained impaired at follow-up. In petrol sniffers with neurobehavioral impairment at baseline, Fisher's exact test showed that nonencephalopathic and encephalopathic sniffers had equivalent rates of complete normalization ($p=0.16$).

Effects of Exposure on Impairment, Improvement and Normalization

The nonencephalopathic group and the encephalopathic group were combined for the following analysis ($n=29$). The number of years sniffing correlated with blood lead level ($r=0.59$; $p=0.002$), total errors on the paired associate learning task at baseline ($r=0.50$; $p=0.01$) and

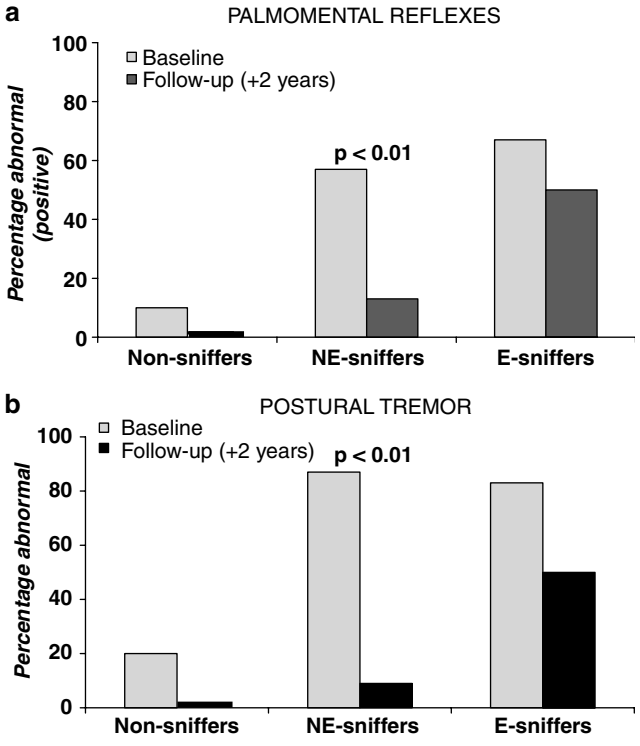

Figure 1 The percentage of individuals from each group who showed neurological abnormalities of (a) palmomental reflex and (b) postural tremor at baseline and follow-up (+ 2 years). *P*-values indicate significant difference in scores between baseline and follow-up for each group; NE = nonencephalopathic, E = encephalopathic.

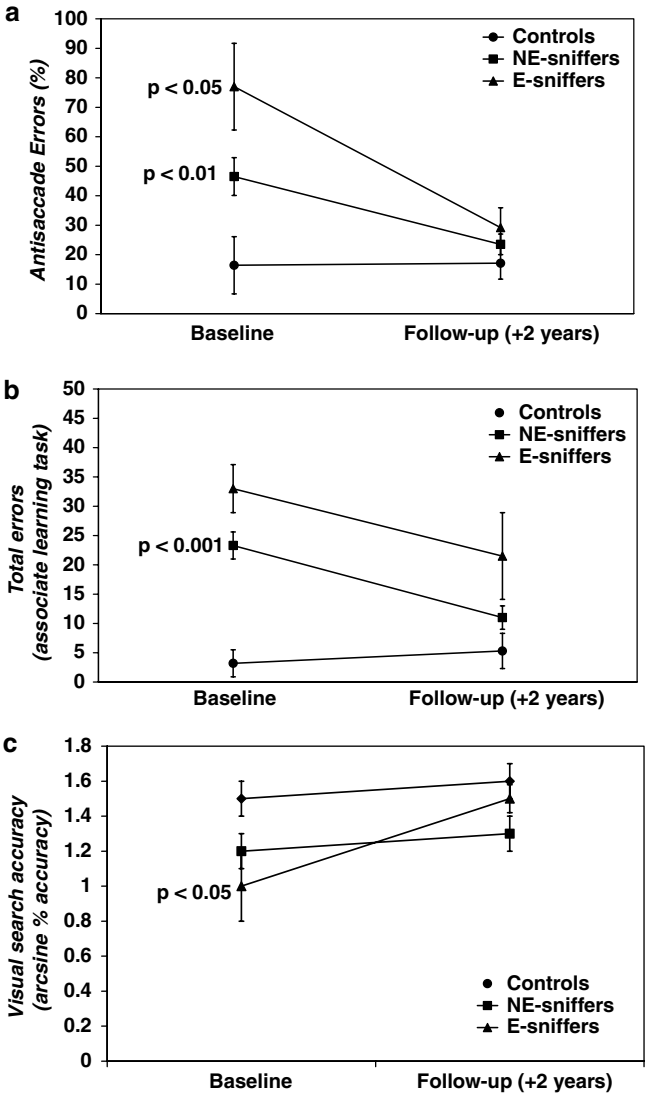

Figure 2 Group mean scores ± SE for (a) antisaccade percentage errors, (b) total errors on the paired associate learning task and (c) visual search accuracy represented at baseline and at follow-up (+ 2 years). Comparison values indicate significant difference in scores between baseline and follow-up for each group; NE = non-encephalopathic, E = encephalopathic.

at follow-up ($r = 0.49$; $p = 0.01$), pattern recognition at baseline ($r = -0.41$; $p = 0.04$), the global abnormality score at baseline ($r = 0.46$; $p = 0.02$) and at follow-up ($r = 0.65$; $p < 0.001$), but did not correlate with the magnitude of improvement or any other neurobehavioral measure. Blood lead level also correlated with total errors on the paired associate learning task at follow-up ($r = 0.46$; $p = 0.01$), visual search accuracy at baseline ($r = -0.47$; $p = 0.01$), pattern recognition accuracy ($r = -0.36$; $p = 0.05$), and the global abnormality score at baseline ($r = 0.52$; $p = 0.004$) and at follow-up ($r = 0.41$; $p = 0.03$). There were no further significant correlations. The global abnormality score at baseline also correlated with the magnitude of improvement ($r = 0.43$; $p = 0.02$). Only those petrol sniffers who showed general neurobehavioral impairment at baseline on the basis of the global abnormality score were included in the following analysis ($n = 22$). To investigate the factors that determine the chance that neurobehavioral impairments will completely recover with abstinence, these individuals were identified as those whose performance normalized by follow-up ($n = 10$) and those whose performance remained abnormal at follow-up ($n = 12$). This analysis showed that petrol sniffers whose neurobehavioral impairment did not normalize with abstinence were older ($t = -4.04$; $p = 0.001$) had sniffed petrol for more years ($t = -2.92$; $p = 0.009$), and showed neurobehavioral impairments that were more severe at baseline ($t = -2.64$; $p = 0.02$) in comparison to petrol sniffers, whose neurobehavioral impairment returned to normal following 2 years of abstinence from petrol sniffing. Blood lead levels did not differ between these groups. At baseline, 91% of nonencephalopathic sniffers showed blood lead levels above the Australian recommended safe limits (0.48 μM/l; National Health and Medical Research Council, 1993) compared to 71% at follow-up. All of the encephalopathic sniffers showed blood lead levels above these limits at both baseline and follow-up.

DISCUSSION

Following 2 years of abstinence from petrol sniffing, individuals with petrol-related CNS dysfunction showed an improvement in neurobehavioral performance that often normalized completely. Blood lead levels in these individuals were significantly reduced over the same period. Prior to the period of abstinence, the severity of abuse correlated with the extent of neurobehavioral impairment,

in accordance with our earlier reports (Maruff *et al*, 1998; Cairney *et al*, 2004a). Individuals who did not show complete recovery with abstinence were usually older had sniffed petrol for more years, and showed more severe neurological impairments prior to abstinence. A history of lead encephalopathy and greater lead body burden were independently associated with more severe neurological impairments although these factors did not appear to influence recovery of CNS dysfunction. In chronic petrol sniffers with no history of lead encephalopathy, our cross-sectional studies have suggested that neurobehavioral function improves with abstinence from petrol sniffing (Maruff *et al*, 1998; Cairney *et al*, 2004a, b). However, in petrol sniffers with a history of lead encephalopathy from severe petrol sniffing, to date there has been no documentation of recovery and no analysis of the factors that contribute to recovery. Importantly, blood lead levels and measures of neurological, saccade, and cognitive function did not change between baseline and follow-up for controls and, for all groups, neurobehavioral functions that were normal at baseline remained normal at follow-up. These data show that petrol-related brain dysfunction ameliorates with abstinence from further abuse and, in fact, may recover completely.

At baseline (prior to abstaining) compared with non-sniffers, chronic petrol sniffers who had never been hospitalized with lead encephalopathy from severe petrol exposure (nonencephalopathic sniffers) showed elevated blood lead levels and neurobehavioral impairments. These impairments were characterized by palmomental reflexes, postural tremor, saccadic disinhibition, impaired associate learning, attentional dysfunction, and impaired recognition memory. Similar to these individuals, all of the ex-petrol sniffers assessed in our previous studies had no history of lead encephalopathy and showed low levels of impairment when performing neurological and cognitive tasks, and no saccade abnormalities (Maruff *et al*, 1998; Cairney *et al*, 2004a). As reported previously, these abnormalities are consistent with fronto-striatal pathologies (Maruff *et al*, 1998; Cairney *et al*, 2004a, b). For example, similar patterns of impairment are observed among individuals with focal cortical lesions or neurodegenerative diseases such as Alzheimer's Disease, and Parkinson's Disease, that disrupt fronto-cortical and basal ganglia pathways (Fletcher and Sharpe, 1986; Vidailhet *et al*, 1994). This suggests that the same brain areas are disrupted in association with chronic petrol sniffing (Maruff *et al*, 1998; Cairney *et al*, 2004a). There was a significant improvement in brain function for nonencephalopathic sniffers, and following 2 years of abstinence from petrol sniffing, recognition memory remained impaired but all other functions were completely returned to normal. Thus, evidence of neurobehavioral recovery in nonencephalopathic sniffers suggests that any disruption to cortical and basal ganglia brain regions caused by chronic petrol sniffing is restored with abstinence.

Consistent with our previous reports, chronic petrol sniffers who had previously been hospitalized with lead encephalopathy from severe petrol exposure (encephalopathic sniffers) showed the same patterns of cognitive impairment as nonencephalopathic sniffers, but also showed higher blood lead levels and more severe neurological abnormalities (Cairney *et al*, 2004a, b). This suggests that cortical and basal ganglia brain regions are also disrupted in encephalopathic sniffers. Additional neurological impairments that were observed among encephalopathic sniffers such as hyperreflexia, ataxic gait, and dysdiadochokinesia also suggest disruption of corticospinal, cerebellar, and brainstem regions in these individuals. Precise ocular motor analysis has previously identified specific cerebellar abnormalities among chronic petrol sniffers with a history of encephalitis that did not occur in nonencephalopathic chronic petrol sniffers (Cairney *et al*, 2004a). Although there was a significant improvement in neurobehavioral impairment following 2 years of abstinence from petrol sniffing, these individuals continued to show residual neurological abnormalities including ataxia, hyperreflexia, dysdiadochokinesia, palmomental reflexes, and postural tremor. Low levels of cognitive impairment also remained including impairments of associate learning and recognition memory. Thus, following 2 years of abstinence from petrol sniffing, encephalopathic sniffers continued to show considerable neurobehavioral impairments that suggest residual fronto-cerebellar and brainstem dysfunction. Similarly, the chronic abuse of alcohol or toluene has also been associated with a gradual decline of brain dysfunction that initially manifests as cognitive impairment, and may graduate to gross physical impairment such as cerebellar ataxia that may be irreversible (Fornazzari *et al*, 1983; Hormes *et al*, 1986; Tuck, 1992). Thus, ongoing investigation is required to determine whether cerebellar degeneration that occurs in encephalopathic petrol sniffers recovers with abstinence beyond 2 years. Furthermore, detection of cognitive impairment in petrol sniffers prior to the occurrence of gross neurological damage may assist with intervention to avoid permanent damage. Comparisons involving encephalopathic sniffers in the current study have reduced statistical power due to the small sample size, and further investigation is therefore needed to confirm these initial observations of neurological recovery in postencephalopathic petrol sniffers. However, clinical observations and neurobehavioral studies also provide converging evidence that lead encephalopathy is associated with a greater severity of petrol-related brain dysfunction (Goldings and Stewart, 1982; Goodheart and Dunne, 1994; Cairney *et al*, 2004a, b). Taken together with our data showing that normalization of brain function is less likely when the level of impairment is greater, this suggests that any incidence of lead encephalopathy from petrol abuse will reduce the chance of neurobehavioral recovery.

Our data suggest that exposure to lead is associated with the extent of neurobehavioral impairment that occurs with petrol sniffing, but is not related to improvement in neurobehavioral function that occurs after a period of abstinence. For example, while there was a significant reduction in blood lead levels corresponding with neurobehavioral improvement for all petrol sniffers following 2 years of abstinence from petrol sniffing, most petrol sniffers still showed blood lead levels above the Australian recommended safe limits (0.48 μM/l; National Health and Medical Research Council, 1993). Leaded petrol contains tetraethyl lead; an organic hydrocarbon with a lead component, which due to its lipid-soluble properties, is absorbed easily by the body and converted rapidly to triethyl lead in the liver (Jensen, 1984). Triethyl lead is

extremely neurotoxic and although it has a half-life in blood of 3-5 days, it is estimated to have a half-life of more than 500 days in brain tissue where there is a high lipid content (Heard *et al*, 1979). In turn, triethyl lead is broken down in the liver to inorganic lead that is partly excreted in the urine and feces, but most of which is preserved in bone where it has a half-life of more than 10 years (Jensen, 1984; Grandjean and Lansdown, 1986). Consequently, lead may continue to be re-released into the bloodstream, even years after the cessation of petrol sniffing (Jensen, 1984). Thus, the improvement in neurobehavioral function despite the prevailing body lead burden with 2 years of abstinence probably reflects some recovery of the initial neurotoxic effects of lead exposure as well as the complicated metabolism of lead (Tenenbein, 1997), rather than that blood lead is unrelated to brain changes in petrol sniffers. Petrol sniffers who participated in this study had inhaled a combination of leaded and unleaded petrol, and were therefore exposed to a combination of toxic hydrocarbons as well as tetraethyl lead. As in our previous studies, it was not possible from these data to make inferences about the relative contribution of lead and hydrocarbons to the various neurobehavioral changes that were observed (Maruff *et al*, 1998; Cairney *et al*, 2004a, b). However, similar patterns of impairment have been observed in solvent abusers exposed to the same hydrocarbons contained in petrol (Sharp and Rosenberg, 1996), suggesting that hydrocarbons contribute significantly to neurobehavioral decline in petrol sniffers. Since the banning of leaded petrol in the study region, there have been no further admissions to the regional hospital with lead encephalopathy from petrol sniffing despite the fact that unleaded petrol sniffing is still a significant problem in many communities (Burns *et al*, 1994b). This supports our previous suggestion that lead is the critical component in the 'petrol sniffer's encephalopathy' or lead encephalopathy that occurs in this particular clinical population (Cairney *et al*, 2004b). Although 'encephalopathy' has been reported in association with the abuse of other inhalants that do not contain lead, the related symptomology is markedly different and less severe than that observed in relation to lead encephalopathy. For example, we previously reported 15 individuals with lead encephalopathy secondary to heavy petrol sniffing who required intensive care hospitalization for an average of 28 days, and on admission presented with average blood lead levels of 4.8 μM/l (range: 1.69–7.25 μM/l; blood lead levels greater than 3.85 μM/l are considered poisonous; Cairney *et al*, 2004b). Owing to its longevity in the body, blood lead may simply be a useful index of exposure to both lead and volatile hydrocarbons, rather than a direct indication of current body lead burden.

To date, there has been no direct evidence that brain dysfunction arising from petrol abuse is recoverable. Here we report that, following 2 years of abstinence from petrol sniffing, neurobehavioral impairments improved and, in many cases, normalized completely. Recovery rates were reduced in individuals with greater exposure to petrol as indicated by longer histories of petrol sniffing, and in those with a greater initial degree of petrol-related brain dysfunction. Petrol contains a varied composition of neurotoxicants, including several volatile hydrocarbons that, either individually or in combination, are also active in other inhalants of abuse. These findings may therefore be applicable to the abuse of other inhalants that contain the same, or similar, active chemicals as petrol. This strong evidence of improvement or complete recovery from petrol-related brain impairment with abstinence promotes a positive message in a health environment often associated with helplessness. Together with observations of increased school attendance and reduced crime rates with abstinence from petrol sniffing (Burns *et al*, 1995a), these findings should encourage clinicians, health professionals, government agencies, and community leaders to focus on strategies and prevention programs that promote abstinence.

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REFERENCES

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington, DC.

Bötzel K, Rottach K, Büttner U (1993). Normal and pathological saccadic dysmetria. *Brain* **116**: 337–353.

Brown A (1983). Petrol sniffing and lead encephalopathy. *NZ Med J* **96**: 421–422.

Brust JCM (1993). Inhalants. In: Brust JCM (ed). *Neurological Aspects of Substance Abuse*. Butterworth-Heinemann: Boston. pp 161–174.

Burns CB, Currie BJ, Clough AB, Wuridjal R (1995a). Evaluation of strategies used by a remote Aboriginal community to eliminate petrol sniffing. *Med J Aust* **163**: 82–86.

Burns CB, Currie B, Currie J, Maruff P (1994b). Petrol sniffing down the track. *Med J Aust* **160**: 729–730.

Burns CB, D'Abbs P, Currie BJ (1995b). Patterns of petrol sniffing and other drug use in young men from an Australian Aboriginal community in Arnhem Land, Northern Territory. *Drug Alcohol Rev* **14**: 159–169.

Burns CB, Sriprakash KS, Powers JR, Currie BJ (1994a). Method for preserving erythrocytic delta-aminolevulinic acid dehydratase activity that facilitates population studies on lead intoxication. *Appl Toxicol* **14**: 365–368.

Cairney S, Clough AR, Maruff P, Collie A, Currie BJ, Currie J (2003). Saccade and cognitive function in chronic kava users. *Neuropsychopharmacology* **28**: 389–396.

Cairney S, Maruff P, Burns C, Currie B (2002). The neurobehavioural consequences of petrol (gasoline) sniffing. *Neurosci Biobehav Rev* **26**: 81–89.

Cairney S, Maruff P, Burns CB, Currie J, Currie BJ (2004a). Saccade dysfunction associated with chronic petrol sniffing and lead encephalopathy. *J Neurol Neurosurg Psychiatry* **75**: 472–476.

Cairney S, Maruff P, Burns CB, Currie J, Currie BJ (2004b). Neurological and cognitive impairment associated with leaded gasoline encephalopathy. *Drug Alcohol Depend* **73**: 183–188.

Clough AR, Baillie R, Burns CB, Guyula T, Wunungmurra R, Wanybarrnga SR (2002). Validity and utility of community health workers' estimation of kava use. *Aust NZ J Public Health* **26**: 52–57.

Coulehan JL, Hirsch W, Brillman J, Sanandria J, Wely T, Colaiaco P *et al* (1983). Gasoline sniffing and lead toxicity in Navajo adolescents. *Paediatrics* **71**: 113–117.

Currie B, Burrow J, Fisher D, Howard D, McEiver M, Burns C (1994). Petrol sniffer's encephalopathy [letter]. *Med J Aust* **160**: 800.

Currie J, McArthur C, Ramsden B, Lynch J, Maruff P (1992). High-resolution eye movement recording in the early diagnosis of Huntington's disease. *Neuropsychiatry Neuropsychol Behav Neurol* **5**: 46–52.

Fletcher WA, Sharpe JA (1986). Saccadic eye movement dysfunction in Alzheimer's disease. *Ann Neurol* **20**: 464–471.

Fornazzari L, Wilkinson DA, Kapur BM, Carlen PL (1983). Cerebellar, cortical and functional impairment in toluene users. *Acta Neurol Scand* **67**: 319–329.

Fortenberry JD (1985). Gasoline sniffing. *Am J Med* **79**: 740–744.

Goldings AS, Stewart RM (1982). Organic lead encephalopathy: behavioral change and movement disorder following gasoline inhalation. *J Clin Psychiatry* **43**: 70–72.

Goodheart RS, Dunne JW (1994). Petrol sniffer's encephalopathy. *Med J Aust* **160**: 178–181.

Grandjean P, Lansdown R (1986). The measurement of lead. In: Lansdown R, Yule W (eds). *The Lead Debate: The Environment, Toxicology and Child Health*. Croom Helm: London. pp 41–53.

Heard MJ, Wells AC, Newton D, Chamberlain AC (1979). Human uptake and metabolism of tetra ethyl and tetra methyl lead vapour labelled with 203Pb. In: *International Conference on Management and Control of Heavy Metals in the Environment*. CEP Consultants: Edinburgh. pp 103–108.

Hormes JT, Filley CM, Rosenberg NL (1986). Neurologic sequelae of chronic solvent vapour abuse. *Neurology* **36**: 698–702.

Jensen AA (1984). Metabolism and toxicokinetics. In: Granjean P (ed). *Biological Effects of Organolead Compounds*. CRC Press: Boca Raton. pp 97–115.

Kurt TL, McAnalley BH, Garriott JC (1982). Lead encephalopathy from gasoline sniffing: successful treatment with chelation. *Tex Med* **78**: 52–54.

Maruff P, Burns CB, Tyler P, Currie BJ, Currie J (1998). Neurological and cognitive abnormalities associated with chronic petrol sniffing. *Brain* **121**: 1903–1917.

Maruff P, Tyler P, Burt T, Currie B, Burns C, Currie J (1996). Cognitive deficits in Machado–Joseph Disease. *Ann Neurol* **40**: 421–427.

Moschner C, Perlman S, Baloh RW (1994). Comparison of oculomotor findings in the progressive ataxia syndromes. *Brain* **117**: 15–25.

National Health and Medical Research Council (1993). Lead in Australians. In: *Report of the 115th session*. NHMRC: Canberra.

Pourcher C, Barbeau A (1980). Field testing of an ataxia scoring and staging system. *Can J Neurol Sci* **7**: 339–344.

Sharp CW, Rosenberg NL (1996). Inhalants. In: Lowinson JH, Ruiz P, Millman RB, Langrod JG (eds). *Substance Abuse: A Comprehensive Textbook*, 3rd edn. Williams and Wilkins: Baltimore. pp 246–264.

Tenenbein M (1997). Leaded gasoline abuse: the role of tetraethyl lead [Review]. *Hum Exp Toxicol* **16**: 217–222.

Tuck R (1992). Alcohol and the brain. *Med J Aust* **156**: 749–750.

Vidailhet M, Rivaud S, Gouider-Khouja N, Pillon B, Bonnet A-M, Gaymard B *et al* (1994). Eye movements in Parkinsonian syndromes. *Ann Neurol* **35**: 420–426.

Wessel K, Moschner C, Wandinger K-P, Kompf D, Heide W (1998). Oculomotor testing in the differential diagnosis of degenerative ataxic disorders. *Arch Neurol* **55**: 949–956.