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Saccade and cognitive impairment associated with kava intoxication

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Kava is an extract from the *Piper methysticum* Forst. f. plant that has social and spiritual importance in Pacific islands societies. Herbal remedies that contain kava are used for the psychiatric treatment of anxiety and insomnia. Laboratory studies have found only subtle, if any, changes on cognitive or motor functions from the acute effects of consuming small clinical doses of kava products. Intoxication from recreational doses of kava has not been studied. The performance of individuals intoxicated from drinking kava ($n = 11$) was compared with a control group ($n = 17$) using saccade and cognitive tests. On average, intoxicated individuals had consumed 205 g of kava powder each (approximately 150 times clinical doses) in a group session that went for 14.4 h and ended 8 h prior to testing. Intoxicated kava drinkers showed ataxia, tremors, sedation, blepharospasm and elevated liver enzymes (GGT and ALP), together with saccadic dysmetria, saccadic slowing and reduced accuracy performing a visual search task that only became evident as the task complexity increased. Kava intoxication is characterized by specific abnormalities of movement coordination and visual attention but normal performance of complex cognitive functions. Saccade abnormalities suggest disruption of cerebellar and GABAergic functions. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — *Piper methysticum*; kava; intoxication; cognitive; saccade

INTRODUCTION

Kava is the name given to products based on root extract from the *Piper methysticum* Forst. f. plant that is native to the Pacific Islands. A beverage form of kava is consumed among indigenous societies in the South Pacific as part of traditional and social practices where it promotes camaraderie and tranquillity. In some Micronesian societies, the calming actions of kava were utilized for the containment of violent individuals (Ashby, 1984). Kava is also important spiritually and is used to facilitate communication with ancestors and gods (Gregory *et al.*, 1983; Lebot *et al.*, 1997). Kava-based herbal remedies have become increasingly popular among industrial societies as naturopathic treatments for anxiety and insomnia (Wong *et al.*, 1998). However, despite these psychiatric applications of kava (Pittler and Ernst, 2000) and the considerable folklore that surrounds its traditional use (Lebot *et al.*, 1997), very little is known about the effects of kava on the central nervous system (CNS; see Cairney *et al.*, 2002 for review).

Anthropological observations in indigenous groups indicate that in small amounts, kava promotes muscle relaxation and sociability (Lebot *et al.*, 1997). As consumption levels increase, kava can cause intoxication

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that is characterized by sedation, analgesia, ataxia, blepharospasm and persistent swallowing with intoxicated individuals eventually falling into an uninterruptible slumber (Lebot *et al.*, 1997; Clough *et al.*, 2000). Kava has been classified as a hallucinogen (Brust, 1993), although these properties of kava have not been proven (Clough, 2001). However, seizures may occur with kava intoxication (Clough *et al.*, 2001). Intoxication has not been reported following ingestion of synthetic kava derivatives that contain comparatively low doses of active kava lactones. However, there have been several isolated case reports of severe choreoathetosis following the use of kava derivatives for the treatment of anxiety and Parkinsonian syndromes (Schelosky *et al.*, 1995). In each case, there was no involvement of other drugs and the symptoms returned to normal following treatment with a sedative. A qualitatively similar choreoathetosis has also been reported in an indigenous male following prolonged and heavy use of crude kava extract (Spillane *et al.*, 1997). On each occasion, these reactions subsided within 12 h of treatment with diazepam. In the early 1980s, kava was introduced to indigenous Australian societies where it was not part of traditional ceremony. While consumption did facilitate social interaction, heavy kava use became endemic in many indigenous communities where quantities consumed are now amongst the highest reported (Clough *et al.*, 2000). Formal studies of these individuals indicate that while chronic kava use is associated with a scaly skin condition known as kava dermopathy (Norton and Ruze, 1994), as well as hepatotoxicity and lymphocytopenia (Mathews *et al.*, 1988; Clough *et al.*, 2003), normal neurobehavioural functions suggest that there are no deleterious effects of chronic kava use on the CNS (Cairney *et al.*, 2003). Therefore, the CNS changes observed with kava intoxication are transient. Laboratory studies of the acute effects of kava on cognitive and motor functions have yielded equivocal results and where behavioural changes are reported, they are always subtle (Saletu *et al.*, 1989; Russell *et al.*, 1987; Münte *et al.*, 1993; Prescott *et al.*, 1993; Heinze *et al.*, 1994; Foo and Lemon, 1997; see Cairney *et al.*, 2002 for review). However, the doses of kava consumed by intoxicated indigenous peoples can be up to 150 times greater than those used in laboratory studies (Cairney *et al.*, 2002). Thus, the laboratory studies provide no real basis for understanding the acute effects of kava on the CNS. Therefore cognitive and saccade function was investigated in a group of indigenous kava users who were acutely intoxicated at the time of testing.

MATERIALS AND METHODS

Participants

The demographic, physical and biochemical characteristics of participants in this study are represented in Table 1. The classification for severity measures of kava consumption and the presence of behavioural characteristics of acute intoxication among participants were made on the basis of consensual ratings from the participant and local community health workers who resided in the same communities (Mathews *et al.*, 1988; Burns *et al.*, 1995; Maruff *et al.*, 1998; Clough *et al.*, 2002; Cairney *et al.*, 2003). Dosage levels were derived from estimates of the number of bags containing 45–75 g of kava powder that participants consumed. The kava intoxicated group included 11 individuals who had consumed a large amount of kava within the 24 h prior to testing. These individuals were all from the same community and had all commenced their kava drinking session 24 h prior to testing. The time spent drinking kava had lasted on average 14.4 h (range 7–22) and the individuals had finished drinking kava 8 h (range 2–17) prior to testing. In this setting, the kava beverage is consumed from a communal bowl and shared equally amongst all members of the kava gathering and thus the consumption rate is similar for all drinkers (Clough *et al.*, 2000). On average, each individual consumed a total of 205 g (range 75–375) kava powder and the average consumption rate was 16.4 g/h kava powder. The control group consisted of 17 regular kava users who had consumed kava within the month prior to testing but had consumed no kava in the week prior to testing. No participant included in the study had a history of seizures, head injury with loss of consciousness or psychiatric illness. No participant who regularly used alcohol consumed more than 800 ml of pure ethanol per month and no participant who regularly used cannabis consumed more than approximately 0.9 g THC per week (see Cairney *et al.*, 2003). No participant had consumed either alcohol or cannabis within 24 h of testing. A memorandum of understanding between the local Aboriginal Community Council and the Menzies School of Health Research guided the research. The Institutional Ethics Committee of the Menzies School of Health Research and Royal Darwin Hospital with input from an Aboriginal subcommittee granted ethical approval. All participants gave written informed consent to the studies.

Procedure

Biochemical and physical tests. Biochemical, physical, behavioural, saccade and cognitive measures

Table 1. Demographic, biochemical, physical and behavioural variables in controls and intoxicated kava users

	Controls ($n = 17$)	Kava intoxicated ($n = 11$)	p-value	Cohen's d
Demographic measures				
Age	33.1 ± 7.0	38.1 ± 10.3	NS	−0.59
Age range	(25–46)	(26–57)		
Males, females	15,2	9,2	NS[a]	
No. past petrol sniffers	2	4	NS[a]	
No. alcohol users	13	6	NS[a]	
No. cannabis users	8	5	NS[a]	
Kava dosage (g/week)	345 ± 150	245 ± 165	NS	0.64
No. years kava use	11.4 ± 6.2	12.9 ± 5.0	NS	−0.26
Physical measures				
Kava dermopathy (n)	6	7	NS[a]	
BMI[b]	19.0 ± 2.6	20.7 ± 5.6	NS	−0.42
Biochemical measures				
Lymphocytes ($\times 10^9$/l)	1.5 ± 0.5	1.8 ± 0.8	NS	−0.47
(% abnormally low)	47.1	45.5	NS	
GGT (U/l)	77.4 ± 52.9	93.7 ± 63.3	NS	−0.29
(% abnormally high)	47.1	<72.7	0.002	
ALP (U/l)	125.9 ± 28.1	$<158.1 \pm 36.7$	0.01	−1.02
(% abnormally high)	41.2	< 63.6	0.001	
Behavioural observations				
Ataxia	0	<5	0.005[a]	
Tremors	1	<6	0.007[a]	
Sedation	0	<5	0.005[a]	
Disorientation	0	2	NS[a]	
Blepharospasm	1	< 6	0.007[a]	

Unless otherwise stated, data are shown as group mean ± SD. NS, not significant. p-values determined with t-test for significance.
[a]Determined with Fisher's exact test for non-parametric statistics.
[b]As this measure is likely to be influenced by gender, comparative analysis was performed on the males only.

taken for this study were identical to those taken in our study of long-term kava users and these procedures have been described in detail previously (Cairney *et al.*, 2003; Clough *et al.*, 2003). For each participant, these measures included the collection of blood for analysis of lymphocytes and the liver enzymes, γ-glutamyl transferase (GGT) and alkaline phosphatase (ALP), the recording of sitting and standing heights and body weight to calculate a body mass index (BMI), physical examination for the presence of kava dermopathy (Norton and Ruze, 1994) and observations of behavioural characteristics consistent with kava intoxication.

Saccade tests. Participants were required to make *visually guided saccades* to fixate random targets; moving with unpredictable direction, amplitude (±15 degrees), and timing (range 1.5–2.5 s). For each participant, saccade latency was calculated as the duration from the onset of the target to the onset of the saccade, and saccade accuracy was calculated as the displacement of the final eye position with respect to the target position. The duration and peak velocity for visually guided saccades were plotted against saccade amplitude. Saccade recordings were examined 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; square wave jerks where a saccadic intrusion is followed by a corrective saccade bringing the eye back to the target and this process may be repeated successively; and gaze-evoked nystagmus which shows difficulty maintaining eccentric fixation of the target (±10 and ±15 degrees) characterized by an alternation between slow drift and corrective quick movements of the eye. For the *antisaccade* task, participants were asked to fixate a central green light-emitting diode (LED; 16.9 cd/m^2) target which was offset simultaneous with the appearance of a peripheral red target, at either ±10 or ±15 degrees. Individuals were instructed to inhibit a reflexive saccade to the peripheral red target and instead, to generate an antisaccade to its mirror location and hold fixation until the green LED reappeared in the centre. Displacement and timing (3.0–3.5 s after fixation) of the appearance of the peripheral red target was random. A correct antisaccade response was an initial eye movement away from the midline to the side opposite to that of the peripheral red target. Any initial reflexive eye movement towards the target was scored

as incorrect, 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 rate was calculated.

Cognitive tests. The cognitive test battery was drawn from the touchscreen based Cambridge Automated Neuropsychological Test Battery (CANTAB). Methods for the use of these tests in indigenous groups has been described previously (Maruff *et al.*, 1996, 1998). Briefly, for the *motor function* task, individuals were required to use their dominant hand to touch the middle of a cross that was presented with random timing and at random locations on the computer screen. Twelve trials were administered following 12 practice trials. The accuracy and latency of hand movements to touch the computer screen were recorded. The *visual search* task began with a central box displayed on the computer screen, surrounded by eight additional boxes. The target, a complex abstract pattern consisting of four different colours, then appeared in the central box and remained visible until the end of the trial. After a 2 s delay, an array of either two or eight similar abstract patterns, one of which was the initial target, appeared in the surrounding boxes. The target therefore appeared with either one or seven similar distracters. Individuals were required to identify which of the (two or eight) surrounding boxes contained the target pattern as quickly as possible by lifting their dominant hand from the response pad and touching the appropriate box. Response times, movement times and the number of correct hits were recorded. In the *pattern recognition* task, 12 abstract target patterns were presented sequentially for 2 s each in the centre of the computer screen. After a 3 s delay, two patterns were then presented simultaneously on the screen, one from the initial 12 targets and one novel, but similar pattern. Individuals were required to touch the target pattern. Twelve pairs of stimuli, each containing a target and a distracter, were shown and the entire procedure was then repeated with a new set of 12 target patterns. The number of patterns recognized correctly was recorded. Finally, in the *pattern-location paired associate learning* task, eight boxes were presented at locations around the edge of the computer screen that were equidistant from the centre. At the beginning of a trial, each box opened for 2 s, in random order, to reveal that it contained either an abstract pattern or was empty. Each box closed after 2 s so that its contents were no longer visible. Individuals were then instructed to remember which of the boxes contained a pattern and what that pattern was. After all of the boxes had opened and closed, a single pattern was presented at the centre of the computer screen, which was identical to one of the patterns that the subject had just been shown. The individual was required to touch the box that contained the identical pattern. Another of the recently shown patterns was then presented in the centre of the computer screen, and again the individual was required to touch the box that had contained that pattern. This was repeated until all the pattern-location associations that made up the trial had been remembered correctly. If an error was made, the same set of pattern-location associations was shown to the individual again and the learning procedure was repeated. Individuals were required to learn sets of one, two, three, six or eight pattern-location associations to complete each test. Individuals were allowed up to 10 repeated trials to learn a single set of pattern-location associations. If the set of pattern-location associations was not learned within 10 trials the set was stopped. The number of trials and errors for each test was recorded.

Data analysis

Demographic, physical, biochemical and behavioural indices of kava drinking and saccadic and cognitive measures were compared between groups using *t*-tests of significance. Where variables did not meet the assumptions for parametric statistics after transformation or where data were categorical, scores were submitted to Mann-Whitney *U* or Fisher's exact test to compare groups. For each group, the percentage of individuals with measures of biochemistry outside the normal reference range ($<1.5 \times 10^9$/l for blood lymphocytes; >135 U/l for ALP; >40 U/l for GGT in females and >60 U/l for GGT in males) were calculated and submitted to chi-square (χ^2) analysis to compare groups. For all participants, saccade amplitudes were <50 degrees. In this amplitude range, the saccade duration-amplitude relationship is best represented using a linear function (Becker, 1989) and the saccade peak velocity-amplitude relationship is best represented using a square-root function (Lebedev *et al.*, 1996). 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. For the visual search task where there were two levels of difficulty (e.g. either two or eight items), each level was treated as a repeated variable in an analysis of variance (ANOVA). Before analysis, the distributions of data for each performance measure were inspected for normality and heterogeneity of variance. Where data did not meet

the assumptions for parametric statistics, the distributions of scores were transformed. Logarithmic base 10 (log) transformation was used to transform distributions of raw data that were skewed significantly in the positive direction to normal. This was necessary for the latency data on the cognitive tasks. Accuracy measures on the cognitive tasks that were scored as percentage correct, formed negatively skewed distributions and arcsine transformations were used to normalize these distributions (Maruff *et al.*, 1996, 1998). Data for group differences were represented by the Cohen's *d* statistic which was then used to determine an estimation of the percentage overlap between the two groups (Zakzanis, 2001). The relationship between indices of the severity of kava use (demographic, physical, biochemical and behavioural) and performance on saccadic and cognitive tests were investigated using Pearson's product moment correlation or Spearman's correlation. The level of significance for comparisons within each of the domains assessed was set at 0.05.

RESULTS

Demographic, physical, biochemical and behavioural characteristics

Group means, standard deviations and statistical parameters for demographic, physical and biochemical measures are shown in Table 1. Kava dermopathy was common in both groups. Almost half of each group had decreased blood lymphocytes. Blood levels for GGT and ALP were more commonly elevated in the intoxicated group compared with controls, as were behavioural observations of intoxication including ataxia, tremors, sedation and blepharospasm. There were no other group differences for any demographic, physical, biochemical or behavioural measure.

Saccade tests

Group means, standard deviations and statistical parameters for each of the saccade and cognitive measures are shown in Table 2. In comparison with controls,

Table 2. Saccade and cognitive performance measures in controls and intoxicated kava users

	Controls ($n = 17$)	Kava intoxicated ($n = 11$)	*p*-value	Cohen's *d*
Saccade measures				
Visually guided saccades				
Gaze-evoked nystagmus[a]	0	0	NS	
Square wave jerks[a]	2	9	NS	
Saccadic intrusions[a]	3	7	NS	
Post-saccadic drift[a]	2	4	NS	
Hypometric (%, range)	7.5 (0–25)	<14.7 (3–29)	0.02[b]	
Hypermetric (%, range)	6.4 (0–24)	3.6 (0–11)	NS[b]	
Anticipations (%, range)	11.5 (0–67)	16.9 (0–71)	NS[b]	
Latency (ms)	175.6 ± 15.1	190.6 ± 30.6	NS	−0.67
Accuracy (%)	100.1 ± 5.1	$>95.8 \pm 3.8$	0.03	0.93
Peak velocity (coefficient)	160.6 ± 34.4	$>135.6 \pm 29.6$	0.05	0.77
Duration (ampl. gradient)	2.0 ± 0.4	2.2 ± 0.4	NS	−0.50
Antisaccades				
Latency (ms)	290.3 ± 76.8	317.4 ± 71.4	NS	−0.36
Error rate (%)	24.8 ± 18.9	29.0 ± 19.2	NS	−0.22
Cognitive measures				
Simple reaction time				
(log latency)	2.88 ± 0.11	2.93 ± 0.14	NS	−0.41
Pattern recognition				
(log latency)	3.58 ± 0.23	3.58 ± 0.22	NS	<0.001
(arcsine % correct)	0.82 ± 0.20	0.72 ± 0.27	NS	0.44
Visual search accuracy (arcsine % correct)				
With 2 pairs	1.51 ± 0.17	1.49 ± 0.19		0.11
With 8 pairs	1.42 ± 0.28	$>1.02 \pm 0.42$	0.01[c]	1.17
Paired associative learning				
Total errors	26.6 ± 15.9	37.1 ± 18.0	NS	−0.63
List memory score	14.8 ± 3.9	12.4 ± 5.8	NS	0.51

Unless otherwise stated, data are shown as group mean ± SD. NS, not significant.
[a]Scored as the number of individuals from each group who show these saccade characteristics; *p*-values determined with *t*-test for significance.
[b]Determined with Mann–Whitney *U*-test for non-parametric statistics).
[c]Determined with repeated measures ANOVA.

Table 3. Correlations between biochemical and behavioural severity measures and saccade and cognitive characteristics

	Duration since last drink	ALP (U/l)	Lymphocytes ($\times 10^9$/l)
Hypometric saccades (%)	-0.48^b	NS	NS
Saccade accuracy (%)	0.55^b	NS	NS
Saccade latency	NS	NS	0.48^a
Pattern recognition (% correct)	NS	-0.41^a	NS
Paired associative learning (total errors)	-0.43^a	NS	NS
Visual search 8 shape condition (% correct)	0.55^b	NS	-0.50^b

$^a p < 0.05$; $^b p < 0.01$; $^c p < 0.001$.

intoxicated individuals demonstrated a decrease in saccade peak velocity shown as a decrease in the velocity coefficient and dysmetria shown as an increase in the proportion of hypometric saccades and a decrease in saccadic accuracy. From the Cohen's *d* statistic, the overlap between the groups was estimated to be 48.4% for saccade accuracy and 52.6% for saccade peak velocity (e.g. Zakzanis, 2001). No other measure of saccadic function differed between the groups.

Cognitive tests

For the visual search task, a significant group by task difficulty interaction showed that, although there was no difference between the groups for accuracy on the 2 pair condition ($t(26) = -0.38$; $p = 0.71$), intoxicated individuals showed a decreased accuracy on the 8 pair condition compared with controls ($t(26) = -3.02$; $p = 0.006$). Furthermore, the Cohen's *d* statistic of 1.17 for this group difference indicated that there was 37.8% overlap between the two groups (e.g. Zakzanis, 2001). No other measure of cognitive function differed between the groups.

Relationship between the severity of kava use and saccadic and cognitive measures

For intoxicated individuals, the liver enzyme ALP correlated with both the duration of the kava drinking session ($r = 0.71$; $p = 0.02$) and the duration from the conclusion of the session to the time of testing ($r = -0.71$; $p = 0.02$). There were no further correlations between different severity measures or between severity measures and saccade or cognitive data for the intoxicated group alone. To investigate the variation in saccadic and cognitive performance measures with indicators of the severity of regular kava use, correlation analysis was performed for two groups combined (see Table 3). When combined with data from non-intoxicated controls, ALP also correlated negatively with the duration since last drinking kava ($r = -0.48$; $p = 0.01$) and this suggests that ALP serves as a biochemical indicator of the recency of kava use. The duration since last drinking kava did not correlate significantly with GGT or blood lymphocyte level. The liver enzyme ALP also correlated inversely with accuracy on the pattern recognition memory task ($r = -0.41$; $p = 0.03$). The duration since last drinking kava correlated significantly with the proportion of hypometric saccades ($r = -0.48$; $p = 0.007$), saccade accuracy ($r = 0.55$; $p = 0.002$), total number of errors on the pattern-location paired associative learning task ($r = -0.43$; $p = 0.02$) and the 8 shape condition of the visual search task ($r = 0.46$; $p = 0.02$). Blood lymphocyte level also correlated with saccade latency ($r = 0.48$; $p = 0.02$) and accuracy on the 8 shape condition of the visual search task ($r = -0.50$; $p = 0.01$). There were no other significant correlations between parameters.

DISCUSSION

Compared with regular kava users who were not intoxicated, individuals who used kava and were intoxicated at the time of testing showed subtle but significant impairment in saccadic and visual attentional function. Importantly, complex and difficult cognitive operations such as those required for performance of the antisaccade and paired associate learning tasks were not disrupted by kava intoxication. The classification of kava intoxication was based on individuals' self reported recent kava consumption, the report of a confederate (e.g. using the established consensual methodology; Mathews *et al.*, 1988; Burns *et al.*, 1995; Maruff *et al.*, 1998; Clough *et al.*, 2002; Cairney *et al.*, 2003) and a rating of behaviours consistent with kava intoxication (Lebot *et al.*, 1997; Clough *et al.*, 2000). The classification of individuals as acutely intoxicated by kava was validated by elevated levels of the liver enzymes, γ-glutamyl transferase (GGT) and alkaline phosphatase (ALP) that were detected in the blood of the intoxicated kava users. In contrast, GGT and ALP levels in the controls did not show the same elevation and corresponded with those of similar groups from our previous studies (Cairney *et al.*, 2003; Clough *et al.*, 2003). Elevated GGT and ALP are sensitive indicators of abnormal liver function. Kava-containing herbal products have been recently associated with severe hepatic toxicity with some fatalities due to hepatic failure, and are

consequently withdrawn from sale in many European countries and the United States (Escher *et al.*, 2001; Centers for Disease Control and Prevention, 2002; Gow *et al.*, 2003). However, elevated GGT and ALP in heavy kava users were not accompanied by elevated aminotransferase (ALT) levels indicative of acute liver inflammation (Clough *et al.*, 2003) and therefore, were not consistent with reported cases of severe hepatoxicity linked with the use of kava herbal products (see Currie and Clough, 2003). The pathological significance, if any, of the elevated GGT and ALP in the absence of elevated ALT remains to be determined. Interestingly, fulminant hepatic failure has not been documented with traditional kava use in Pacific countries or among Australian Aboriginal populations where consumption levels are considerably greater than recommended therapeutic doses of kava herbal products (Moulds and Malani, 2003; Currie and Clough, 2003). In the current intoxicated group, the amount of kava consumed to achieve their intoxicated state was also very high with individuals consuming on average 205 g of kava powder prior to testing. Based on estimates of kava lactone concentration that were developed previously (Clough *et al.*, 2000), intoxicated individuals in the current study had consumed 25 g of kava lactones. This is approximately 150 times the daily dose given in natural kava supplements. Taken together the current data indicate that acute kava intoxication is associated with observable behavioural, biochemical and neurobehavioural changes. Importantly, these individuals were not so intoxicated that they were unable to move from the site of drinking kava. Despite movement and attentional abnormalities, they were capable of coordinating their attendance and participation in the testing session. These results also contrast completely with the normal neurobehavioural function observed previously in non-intoxicated but chronic kava users using the same assessments.

Disruption to saccades as a consequence of kava intoxication was characterized by dysmetria and slowing of visually guided saccades. The dysmetria manifests as both an increase in the proportion of hypometric saccades made in response to visual targets as well as an average reduction in the accuracy of all visually guided saccades. The saccadic slowing was characterized by a reduced peak velocity of visually guided saccades, although the latency of visually guided saccades was not affected by kava intoxication nor was their duration. Saccade peak velocity is sensitive to the acute effects of sedating drugs including benzodiazepines, barbiturates, anticonvulsants and alcohol and is considered a valuable indicator of the pharmacological effects mediated by the GABA-benzodiazepine receptor complex (Jürgens *et al.*, 1981; Thurston *et al.*, 1984; Richens *et al.*, 1993; Cowley *et al.*, 1994; Kroboth *et al.*, 1998; Moser *et al.*, 1998). An interaction between kava lactones and GABAergic systems is well established in animal studies that show kava lactones cause alterations to the GABA-benzodiazepine receptor complex through their direct actions on sodium-dependent ion channels (Duffield and Jamieson, 1988; Davies *et al.*, 1992; Jussofie *et al.*, 1994; see Cairney *et al.*, 2002 for review). However, this is the first strong behavioural evidence of such an interaction in humans. Importantly, there was no evidence of saccadic disinhibition, nystagmus or abnormal accuracy or latency of antisaccades that are usually observed in humans who have ingested stimulants that disrupt dopaminergic frontostriatal neural networks (Tedeschi *et al.*, 1983; Hotson *et al.*, 1986; Dursun *et al.*, 1999; Klein *et al.*, 2002; Vassallo and Abel, 2002). The pattern of saccade slowing and dysmetria together with normal saccade latency and normal antisaccades (error rate and latency) that was observed among intoxicated kava users is similarly observed among humans with cerebellar abnormalities due to degenerative ataxic disorders (Moschner *et al.*, 1994; Buttner *et al.*, 1998; Wessel *et al.*, 1998) and among humans and animals with cerebellar lesions (Bötzel *et al.*, 1993; Barash *et al.*, 1999). Interestingly, neuronal activity within the cerebellum and from the cerebellum to brainstem saccade generators are modulated by GABA (Büttner and Fuhry, 1995). The importance of GABA in the modulation of saccade metrics is highlighted by animal studies that show saccadic dysmetria occurs as a consequence of cerebellar injection of the the GABA-agonist muscimol (Goffart and Pelisson, 1998; Robinson, 2000). This suggests strongly that kava related movement disorders may reflect disruption to the cerebellum and may involve GABAergically modulated functions.

The only cognitive impairment observed in individuals acutely intoxicated with kava was a decline in the accuracy of visual attention under a high load. Tasks that required more basic psychomotor functions (e.g. reaction time) as well as more demanding memory tasks (e.g. paired associative learning) were performed normally despite the intoxicated state. Together with the saccade data, this suggests that kava acts to disrupt motor coordination but does not interfere with the initiation of movement, and impairs the ability to maintain high levels of visual attention but does not interfere with other cognitive functions. These observations accord with previous clinical

investigations where movement abnormalities and slight attentional variations were reported, but no further cognitive impairments were found in healthy individuals who were given lower but acute doses of kava (Saletu *et al.*, 1989; Russell *et al.*, 1987; Münte *et al.*, 1993; Prescott *et al.*, 1993; Heinze *et al.*, 1994; Foo and Lemon, 1997). The specific nature of the cognitive and saccadic abnormalities observed also suggest strongly that kava acts on specific brain systems associated with motor coordination and visual attention rather than inducing a generalized confusion and delirium as occurs with high levels of alcohol intoxication (Charness *et al.*, 1989; Brust, 1993). It also corresponds to the main aspects of abnormal behaviour that are observed in individuals intoxicated from heavy kava use, who continue to have sensible thought processes and comprehensive conversations yet have difficulty coordinating movement and often fall asleep eventually at the same location where they had been drinking kava (Singh, 1992; Lebot *et al.*, 1997; Clough *et al.*, 2000). Interestingly the main effect of kava reported by individuals who have been intoxicated is that while their body relaxes their mind remains clear (Lebot *et al.*, 1997). Similarly, intoxicated individuals in the current study showed saccade abnormalities that indicated problems with motor coordination yet their cognitive performance was equivalent to controls suggesting that despite their intoxicated state, their thought processes remained clear. Thus the predominant feature of kava intoxication is motor incoordination that is accompanied by a slight and specific visual attentional deficit. The absence of any saccade or cognitive changes following up to 18 years of near daily recreational kava consumption that was reported previously (Cairney *et al.*, 2003) suggest strongly that the neurobehavioural changes reported in the current study were solely due to acute kava toxicity. Thus, intoxication from heavy kava consumption is associated with motor and attentional abnormalities that are normalized once kava lactones are metabolized and cleared from the body.

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