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Attention to pleasant stimuli in early adolescence predicts alcohol-related problems in mid-adolescence

Joshua B.B. Garfield[a], Nicholas B. Allen[b,c,e], Ali Cheetham[a], Julian G. Simmons[b,d], Dan I. Lubman[a,*]

[a] Turning Point, Eastern Health and Monash University, 54-62 Gertrude Street, Fitzroy, VIC 3065, Australia
[b] Melbourne School of Psychological Sciences, The University of Melbourne, Parkville, VIC 3010, Australia
[c] Orygen Youth Health Research Centre, Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC 3010, Australia
[d] Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, VIC 3052, Australia
[e] Department of Psychology, University of Oregon, Eugene, USA

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ABSTRACT

Attenuated responses to natural rewards have been found to predict subsequent substance use among dependent populations, suggesting that this may be a premorbid risk factor for later problematic substance use. However, research on adolescent risk-taking suggests that exaggerated, rather than blunted, reward responsiveness predicts later substance abuse. Acoustic startle-induced event-related potentials (ERP) were recorded in a sample of 11–13 year-olds while they viewed affective pictures, and participants were reassessed four years later regarding alcohol use and experience of alcohol-related problems. Increased attenuation of the amplitude of the P300 component of the ERP during viewing of pleasant pictures, relative to amplitude during neutral pictures (an indicator of increased attention to pleasant pictures), predicted increased likelihood of alcohol-related problems at follow-up. These findings further support research indicating that increased reward responsiveness predicts risky behaviours in adolescence, with anhedonia primarily a consequence of substance dependence.

1. Introduction

There is growing evidence that reduced responsiveness to natural reinforcers predicts future drug use among substance-dependent samples. Specifically, reduced responsiveness to pleasant images has been found to correlate with increased alcohol cravings in detoxified alcoholics (Wrase et al., 2007) and to predict higher levels of substance use over the subsequent 6 months in samples dependent on alcohol (Heinz et al., 2007), heroin (Lubman et al., 2009), and tobacco (Versace et al., 2012). Utilising event-related potential (ERP) indices of attention to pleasant, unpleasant, neutral, and drug-related pictures, Lubman et al. (2009) found that in opioid-dependent participants, reduced attention allocation to pleasant pictures (relative to heroin-related pictures) predicted increased likelihood of frequent (weekly or more) heroin use 6-months later. Similarly, Versace et al. (2012) found that in smokers attempting to quit tobacco, a pattern of ERP responsiveness characterised by reduced attention to pleasant (but not unpleasant, neutral, or cigarette-related pictures) predicted reduced likelihood of abstinence at 10-, 12-, and 24-week follow-ups. Further support for such findings comes from an fMRI study of alcoholics tested 1–3 weeks after detoxification (Heinz et al., 2007) which found that reduced blood-oxygenation level dependent (BOLD) activation in structures associated with reward processing and response (i.e., thalamus and ventral striatum) to pleasant vs. neutral pictures predicted a higher number of drinking days over the following 6 months. In contrast, activation to alcohol-related or unpleasant pictures did not predict later alcohol consumption. Wrase et al. (2007) also found that alcoholics tested after 5–37 days abstinence showed reduced BOLD response in the ventral striatum, relative to healthy controls, during monetary reward expectation, and that lower BOLD responses in the alcoholic group (but not in controls) correlated with increased alcohol craving.

These studies all find that a blunted response to rewarding stimuli increases the likelihood of greater subsequent substance use. However, recent human and animal research suggests that this is more likely to reflect a function of being drug dependent, rather than a premorbid risk factor. For example, studies of sensitivity to

* Corresponding author. Tel.: +61 3 8413 8400; fax: +61 3 9416 3420.
E-mail addresses: joshuag@turningpoint.org.au (J.B.B. Garfield), nallen3@uoregon.edu (N.B. Allen), alisonc@turningpoint.org.au (A. Cheetham), jgs@unimelb.edu.au (J.G. Simmons), dan.lubman@monash.edu (D.I. Lubman).

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lateral hypothalamic stimulation reward in rats after withdrawal from prolonged administration of alcohol (Schulteis, Markou, Cole, & Koob, 1995), amphetamine (Lin, Koob, & Markou, 1999), cocaine (Ahmed, Kenny, Koob, & Markou, 2002; Kenny, Polis, Koob, & Markou, 2003), nicotine (Skjei & Markou, 2003), and phencyclidine (Spielewoy & Markou, 2003) have consistently found that the magnitude and/or duration of the impairment of reward responsiveness increases with the dose and/or duration of drug administration.

According to the reward allostasis model (Koob & Le Moal, 2008), neural adaptations to chronic over-activation of reward circuitry during drug use underlie this impaired reward responsiveness. These adaptations manifest as dysphoria and anhedonia when the drug is withdrawn, motivating further substance use to "self-medicate" this reward deficit. Consistent with this model, there is evidence from human studies that anhedonia increases following the onset of substance abuse (Bovasso, 2001), predicts increased likelihood of relapse in dependent users attempting to quit (Cook, Spring, McChargue, & Doran, 2010; Leventhal, Waters, Kahler, Ray, & Sussman, 2009), and declines over time with successful abstinence in those recovering from substance dependence (Dawes, Sitharthan, Conigrave, Phung, & Weltman, 2011; Dawkins, Powell, Pickering, Powell, & West, 2009; Martinotti et al., 2011; McGregor et al., 2005; Newton, Kalechstein, Duran, Vansluis, & Ling, 2004).

Taken together, these findings suggest that impaired reward responsiveness is likely to emerge alongside the development of a substance use disorder, and may diminish with abstinence. This does not exclude the possibility that low reward responsiveness *prior* to onset of substance use could function as a premorbid risk factor, increasing vulnerability to heavy or frequent substance use later in life. However, research on adolescent risk-taking suggests that exaggerated, rather than blunted, reward responsiveness may predict initial onset of substance use and abuse. Exaggerated reactivity to reward in adolescence is widely reported (for a review, see Spear, 2011), and it has been argued that this enhanced reward reactivity may increase the likelihood of risky behaviour (including substance use) through its effects on the relative attribution of benefit vs. cost to an activity (Spear, 2011). Indeed, in a cross-sectional fMRI study of adolescents aged 13–17, Galvan, Hare, Voss, Glover, and Casey (2007) found that BOLD response in the nucleus accumbens (a key component of the reward circuit) to monetary reward correlated positively with self-reported likelihood of future engagement in risk-taking activities and anticipated positive consequences of such activities, while correlating negatively with anticipated negative consequences of such risky activities. Regarding substance use specifically, a longitudinal study (Stice, Yokum, & Burger, 2013) found that, in adolescents with no history of substance use at baseline (mean age 15.3), increased dorsal striatal response to monetary reward predicted increased likelihood of onset of substance use in the following year. Adolescents who already had a history of substance use at baseline showed lower striatal response to monetary reward than those with no substance use history, further supporting a model whereby increased reward response predicts onset of substance use but, once substance use is commenced, it causes blunting of reward response.

It is unclear whether the relationship between exaggerated reward response and substance use would also be present in adults with no prior history of substance use, or whether it is specific to adolescence. This is difficult to determine in practice because adolescence and early adulthood are associated with the highest rates of substance use onset, with few adults commencing substance use at a later age. Nevertheless, the maturation of striatal reward-related neural systems, and the associated peak in sensation-seeking in adolescence, combined with the incomplete maturation of prefrontal cortical systems (Casey & Jones, 2010; Luciana, Wahlstrom, Porter, & Collins, 2012), may mean that the relationship between reward response and risky substance use is particularly strong in adolescence. The decline in impulsivity, sensation-seeking, and reward-related behavioural activation that accompanies the transition to adulthood (Luciana et al., 2012), along with the final stages of maturation of prefrontal cortical brain structures, could be expected to dampen the relationship between reward response and risky behaviour seen in adolescents (Casey & Jones, 2010).

Prospective research exploring the relationship between adolescent reward responsiveness and substance use remains limited, particularly in terms of predicting later problematic use. To address this gap, we examined attenuation of the acoustic startle-elicited P300 component of the visual event-related potential (ERP) during viewing of pleasant and unpleasant pictures, relative to its amplitude during viewing of affectively neutral pictures, in a sample of 11–13 year-olds, when participants had either no, or extremely limited, previous use of alcohol or other drugs. The amplitude of the P300 indexes allocation of limited attentional resources to the startling stimulus. Its degree of attenuation (amplitude reduction) in the presence of an affective stimulus is thus a measure of the affective stimulus' ability to capture attention (Schupp, Cuthbert, Bradley, Birbaumer, & Lang, 1997).

Participants were assessed for alcohol use outcomes approximately 4 years later, an age at which, despite legal restrictions (the legal drinking age in Australia is 18), over 80% of this sample had at least some experience with alcohol. We were particularly interested in outcomes indicative of risk for alcohol use disorders, including frequent alcohol consumption, binge-drinking, and experience of alcohol-related problems among adolescents who had consumed alcohol. Following Spear (2011), our hypothesis was that greater responsiveness to reward stimuli, as reflected in increased P300 attenuation during viewing of pleasant pictures, would predict frequent alcohol use and alcohol-related problems later in adolescence. Response to unpleasant pictures was also subjected to exploratory analyses. While Spear (2011) suggests that reduced sensitivity to unpleasant stimuli may increase propensity towards risk-taking, there does not appear to be any empirical literature on studies of humans that suggests that it is a predictor of problematic substance use.

2. Methods

2.1. Participants

Participants were recruited from the Orygen Adolescent Emotional Development Study, a longitudinal, multi-method study of adolescents from across metropolitan Melbourne, Australia. Informed consent was obtained from participants and their parents/guardians in accordance with procedures approved by the University of Melbourne Ethics Committee. Further details about recruitment and selection of participants in this study can be found elsewhere (Whittle et al., 2008). Of 240 eligible participants, a subset of 72 (38 males, 34 females; mean age = 12.8 years, SD = .4) was randomly selected to complete baseline EEG assessment. Of these participants, 58 (26 males, 32 females; mean age 16.6, SD = .5) completed the follow-up assessment of alcohol use conducted a mean of 3.8 years (SD = .4) after baseline. There were no significant differences between those that completed the follow-up assessment and those who did not in the P300 parameters subjected to analyses ($ps > .354$), socioeconomic status ($p = .859$), or age at baseline ($p = .176$). However, those who were followed up were more likely to be female than those who were not ($\chi^2 = 7.565$, $p = .006$).

Participants were screened at baseline for current and past case level Axis I disorders by trained research assistants using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version-5 (K-SADS-E-5) (Orvaschel, 1995). Overall, nine participants met criteria for a current psychiatric diagnosis (attention deficit hyperactivity disorder (ADHD), $n = 3$; conduct disorder, $n = 1$; depressive disorder not otherwise specified, $n = 1$; oppositional defiant disorder (ODD), $n = 1$; separation anxiety disorder, $n = 1$; specific (blood/injection/injury) phobia $n = 1$; social phobia, $n = 2$), including one participant who met criteria for two current disorders (ADHD and conduct disorder). Of those nine participants, two met criteria for additional past disorders (one with current ADHD and past ODD, one with current ODD, past ADHD). An additional three participants met criteria only for past psychiatric diagnoses (major depressive disorder (MDD), $n = 1$; obsessive compulsive disorder, $n = 1$; specific (animal) phobia, $n = 1$). Eight of the 12 participants

with any history of psychiatric diagnoses (including seven of the nine with current diagnoses at baseline) completed the follow-up assessment. Drop-outs included one participant with current ADHD only, one with both current ADHD and conduct disorder, one with past MDD, and one with past specific (animal) phobia. No participant met criteria for a substance use disorder.

2.2. Socioeconomic status (SES)

A measure of SES was derived using data on parental occupation at baseline. Occupations were coded according to the ANU-4 scale (Jones & McMillan, 2001), a socioeconomic index derived specifically for the Australian context that classifies occupation based on social and economic characteristics. For parents with missing occupational data, a measure of education was substituted (total years in school, scaled to reflect ANU-4 codes).

2.3. Materials

2.3.1. Affective picture set

The picture set contained 18 unpleasant, 18 pleasant and 18 neutral pictures. Unpleasant and pleasant pictures were selected on the basis of valence and arousal ratings collected in a previous pilot study in which 20 Australian 12–13 year old children (55% male) rated a large selection of pictures, including many from the International Affective Picture System (IAPS) (Lang, Ohman, & Vaitl, 1988), along with other pictures with similar content deemed appropriate for children (sport and cartoon images for pleasant pictures; disaster and dangerous animal pictures for unpleasant). Neutral pictures were IAPS pictures selected based on low arousal and neutral valence ratings in the pilot study. In the pilot study, pictures were rated using a paper and pencil version of the Self Assessment Mannequin (SAM) (Lang et al., 1988) that utilised a 5 point rating scale (ranging from −2 to +2) to rate the valence and arousal properties of each picture. Valence ratings from the pilot study were significantly more negative for unpleasant ($M = -1.29$, SD = .34) than for neutral ($M = .24$, SD = .34; $t(34) = -13.6$, $p < .001$) and pleasant ($M = .97$, SD = .37; $t(34) = -19.0$, $p < .001$) pictures. Pleasant pictures were also significantly more pleasant than neutral pictures ($t(34) = 6.1$, $p < .001$). With respect to arousal ratings, both the pleasant pictures ($M = .60$, SD = .38) and the unpleasant pictures ($M = .65$, SD = .28) were rated as significantly more arousing than the neutral pictures ($M = .14$, SD = .25; $ts(34) = 4.3$ and 5.8, respectively, $ps < .001$), with no significant difference between pleasant and unpleasant picture categories for arousal ratings ($t(34) < 1$). Each picture was presented to participants for 8 s on a 21-in. CRT Sony Trinitron monitor, placed approximately 1 m from participants' knees, such that pictures comprised approximately 24° of visual angle.

2.3.2. Alcohol use measure

At follow-up, participants completed the Youth Risk Behaviour Survey (YRBS) (CDC, 1999). Only data from the alcohol use section was used in the present study. This section indexed total number of days on which at least one alcoholic drink was consumed (lifetime and past 30 days), age of first alcohol consumption, and total number of days on which at least 5 alcoholic drinks were consumed (past 30 days). In addition, participants were presented with a list of 10 specific alcohol-related problems (ARPs) adapted from Little et al. (2012) (see Table 2) and asked to indicate, for each problem, whether or not they had experienced it at least once during the past 12 months as a result of their alcohol use.

2.3.3. Startle probes

Binaural, acoustic startle probes, consisting of a 50 ms burst of 95 dB white noise with immediate rise time, were presented binaurally through Sennheiser HD 280 Pro headphones 2.5 s after picture onset on 12 trials of each picture type. Startle probes were presented either 5 or 7 s post picture offset for 18 trials. Only ERP responses to the 12 probes per picture type that were presented during picture presentation are analysed below. Two picture and startle probe orders, one the reverse of the other, were counter-balanced across participants.

2.4. Procedure

Participants attended the psychophysiology sessions with at least one parent or guardian. An Electro-Cap International EEG cap was fitted to the child and electrodes filled with ECI Electro-Gel conducting gel. Participants were taken into a separate, sound attenuated room and were instructed to attend to each of the pictures and his/her emotional reaction to it. Participants were instructed to ignore the startle probes. At the conclusion of the picture-viewing program, participants received a debriefing and were reimbursed with a $30 gift voucher and parents/guardians reimbursed $50 cash.

2.5. Data processing and reduction

Physiological signals were recorded using a Grass Model 12 Neurodata acquisition system linked to an IBM compatible microcomputer via a PC-Labcard 812-PG analogue-to-digital converter. The VPM 11.0 software package (Cook, 2000) controlled the timing and presentation of stimuli, and collection and storage of the physiological data. The electroencephalogram (EEG) was recorded from 9 scalp sites, based on the international 10–20 system—frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4), with linked earlobes as the reference and forehead as the ground. Vertical electrooculography (EOG) was recorded from electrodes placed above and below the right eye, and horizontal EOG from electrodes placed at the outer canthi of each eye.

Parameters for amplification, filtering, and epoching, of the EEG signal and for ERP waveform peak scoring were as previously described (Lubman et al., 2009). For each probe presentation, EEG and EOG recordings were manually examined for saturation (greater than ±75 μV) and saturated trials excluded from further analyses. All channels were then baseline corrected to the mean of their 150 ms pre-stimulus period. An eye movement artefact correction algorithm (Semlitsch, Anderer, Schuster, & Presslich, 1986) using VEOG channel data was applied within participants for each trial for each EEG channel to correct for vertical ocular artefacts. All data trials were then re-examined and any further saturated trials excluded.

Event-related potential waveforms were then obtained for each individual by averaging the EEG signal each picture category. Due to a high number of movement-related and other artefacts, likely arising from the inherent difficulties of conducting startle research with children, 38.5% of epochs were rejected due to saturation, and numbers of epochs that contributed to ERP averages ranged from 2 to 12 for all picture types (neutral mean = 7.1, SD = 2.5; pleasant mean = 7.8, SD = 2.4; unpleasant mean = 7.5, SD = 2.7). As the startle-induced P300 tends to be a larger, more consistent, waveform than that which appears in the more commonly-studied oddball ERP, several past researchers have published findings regarding startle-induced ERPs averaged from as few as 2–4 trials (Hirano, Russell, Ornitz, & Liu, 1996; Ornitz, Gehricke, Russell, Pynoos, & Siddarth, 2001; Roth, Dorato, & Kopell, 1984; Sugawara, Sadeghpour, De Traversay, & Ornitz, 1994).

Startle-elicited N1, P2, N2, and P300 components were identified combining visual inspection of grand averaged waveforms and a peak-scoring algorithm written in our laboratory, which used the component parameters of Schupp et al. (1997). These components fall in the following time windows: N1 (64–192 ms), P2 (from N1 latency until 272 ms), N2 (from P2 latency until 336 ms) and P300 (from N2 latency until 504 ms). Only data regarding the P300 component were analysed, given that this is the most researched and functionally well-understood probe-elicited ERP component (e.g., Schupp et al., 1997).

2.6. Data analysis

Statistical analysis was undertaken in PASW Statistics 18. Statistical significance was set at $p < .05$. P300 amplitude was analysed at Pz, given past research indicating effects are strongest at parietal sites (exploratory analyses in this study confirmed this). Measures of processing of pleasant compared with neutral (P3Pleas), and unpleasant compared with neutral pictures (P3Unpleas) were calculated by examining residuals generated from univariate regression analyses in which response during pleasant or unpleasant pictures was regressed onto response during neutral pictures. ERP data for all trial types was missing from one participant due to equipment malfunction. In addition, data from pleasant trials only was missing from two participants (one due to equipment malfunction and one due to only one pleasant epoch being available after artefact rejection) and data from unpleasant trials only was missing from two other participants due to equipment malfunction. Thus, analysable data regarding ERP response during pleasant pictures was available for 69 participants (57 of whom completed the follow-up) and data regarding response during unpleasant pictures was available for 69 participants (56 of whom completed the follow-up).

Continuous variables were tested for normality with Kolmogorov–Smirnov tests, with $p < .001$ set as the threshold for considering a distribution to be non-normal. Distributions of age (at both baseline and follow-up), time between baseline and follow-up, SES, and P300 amplitude residuals for both unpleasant and pleasant pictures did not significantly depart from normality (all $ps > .02$). All alcohol-related variables (lifetime number of days of alcohol use, age of first alcohol use, number of days alcohol use in the past 30 days, number of days of risky drinking (defined as ≥5 standard drinks in one day) in the past 30 days, and number of ARPs experiences in the past year) had non-normal distributions.

Within-subjects differences in raw P300 amplitudes were tested with repeated measures analysis of variance. Cross-sectional associations between continuous baseline variables were tested with Pearson correlations. Where differences between groupings of participants were analysed, independent samples *t*-tests or one-way ANOVA with Bonferroni post-hoc tests were used for normally-distributed variables. For non-normal continuous measures, where there were 3 or more groups, Kruskall–Wallis tests were used for between-group comparisons of non-normal variables. Pairwise comparisons (or post-hoc testing after a significant Kruskall-Wallis test result) were analysed with Mann-Whitney *U* tests. Differences in sex distribution were tested with Pearson χ^2 tests.

For regression analyses, lifetime number of alcohol use days was transformed to normality (Kolmogorov–Smirnov $p = .053$) with square root transformation and its relationship to baseline P300 amplitude was analysed with linear regression. Other alcohol outcomes subjected to regression analyses (use, or risky use, in past 30 days; ARPs in past year) had unimodal distributions with large modes at zero, and could therefore not be transformed to normality. These variables were therefore converted into categories for analysis with logistic regression. Association between P300 residuals and binary categorical outcomes (any risky drinking in the past

Table 1
Pearson correlations between variables measured at baseline.

		Age	SES	P3Pleas
SES	*r*	−.201		
	p	.109		
	n	65		
P3Pleas	*r*	−.028	−.009	
	p	.819	.942	
	n	69	65	
P3Unpleas	*r*	−.065	.036	.551*
	p	.595	.781	<.001
	n	69	63	67

SES: socio-economic status; P3Pleas: residual of P300 amplitude during pleasant pictures after linear regression against amplitude during neutral pictures; P3Unpleas: residual of P300 amplitude during unpleasant pictures after linear regression against amplitude during neutral pictures.
* $p < 0.05$.

month, consumption of any alcohol on ≥5 days in the past month, experience of ARPs in the past 12 months) were analysed with binary logistic regression. Number of ARPs reported were further categorised into three categories (0 problems, 1–2 problems, and 3–5 problems) for analysis with ordinal regression with a negative log-log link function (selected because the majority of participants reported no ARPs). Gender was included as a covariate in all regression analyses. Participants who reported never having consumed alcohol at follow-up ($n = 8$) were excluded from analyses of past month (binge drinking and more-than-weekly drinking) and past year (ARPs) alcohol outcomes given the focus on prediction of progression to problematic use among adolescents exposed to alcohol.

3. Results

Grand mean average ERP waveforms at Pz are shown for each picture type in Fig. 1. At baseline, mean P300 amplitude was 8.5 μV (SD = 5.6) during pleasant pictures, 9.9 μV (SD = 5.9) during neutral pictures, and 8.7 μV (SD = 5.7) during unpleasant pictures. Pairwise repeated measures ANOVAs showed significant attenuation of P300 amplitude during pleasant pictures relative to neutral pictures ($F(1, 68) = 5.376$, $p = .023$) and also a trend towards attenuation during unpleasant pictures ($F(1, 68) = 3.112$, $p = .082$). Correlations between baseline P300 amplitude residuals and other baseline variables are shown in Table 1. P300 amplitude residuals were unrelated to age or SES, and also did not differ between those with a lifetime psychiatric diagnosis and those without (P3Pleas: $t(67) = -.832$, $p = .408$; P3Unpleas: $t(67) = -.416$, $p = .679$). P3Pleas and P3Unpleas were significantly positively correlated, suggesting that an individual's tendency for P300 amplitude to be attenuated during emotional pictures of one valence, relative to neutral pictures, was associated with a tendency towards attenuation during pictures of the opposite valence as well.

Of the 58 participants who completed follow-up, 8 reported never having consumed alcohol. Those who had never consumed alcohol did not significantly differ from those who had ($n = 50$) in sex distribution ($\chi^2 = .100$, $p = .751$), age at follow-up ($t(56) = -1.470$, $p = .147$), SES ($t(55) = 1.164$, $p = .249$), presence of a lifetime psychiatric diagnosis ($\chi^2 = .013$, $p = .909$), P3Pleas ($t(55) = -.152$, $p = .879$) or P3Unpleas ($t(54) = .196$, $p = .845$). Those who consumed alcohol reported a median age of first consumption of 14 years (range: 9–16, $n = 42$ due to missing data for 8 participants). Of the 50 who reported having ever consumed alcohol, 22 reported binge drinking in the month prior to follow-up. Past month binge drinkers did not significantly differ from non-binge drinkers ($n = 28$) in sex distribution ($\chi^2 = .930$, $p = .335$), age at follow-up ($t(48) = -1.619$, $p = .112$), SES ($t(47) = -.607$, $p = .547$), presence of a lifetime psychiatric diagnosis ($\chi^2 = .004$, $p = .948$), or age of first alcohol consumption ($U = 163.0$, $p = .130$). Binge drinkers did, however, report a higher number of lifetime days on which alcohol was consumed than non-binge drinkers (binge drinker median = 35, IQR = 20–50; non-binge drinker median = 11, IQR = 4.25–20; $U = 119.5$, $p = .001$). Twelve participants reported 5 or more days on which alcohol was consumed during the past month, and were classified as more-than-weekly drinkers. More-than-weekly drinkers did not differ from less-than-weekly drinkers ($n = 38$) in sex distribution ($\chi^2 = 1.317$, $p = .251$), age at follow-up ($t(48) = -.165$, $p = .869$), SES ($t(47) = .816$, $p = .418$), or age of first alcohol use ($U = 117.5$, $p = .213$). However, more-than-weekly drinkers reported significantly more lifetime drinking days than less-than-weekly drinkers (more-than-weekly drinkers median = 40, IQR = 20–50; less-than-weekly drinkers median = 15, IQR = 6.25–23.75; $U = 111.5$, $p = .012$) and were significantly more likely to have had a lifetime psychiatric diagnosis at baseline ($\chi^2 = 4.902$, $p = .027$).

Table 2
Frequency of alcohol-related problems and of overall number of problems reported.

Alcohol-related problem	Number of participants reporting this problem
Getting so drunk you were sick or passed out	15
Being unable to remember what happened the night before	14
Having trouble at home, work, or school	5
Feeling you were not able to stop drinking once you started	4
Getting into trouble with the police	3
Being asked to leave a party, pub, or club because you were drunk	2
Becoming violent and getting into a fight	1
Feeling irritable or depressed when alcohol wasn't available	1
Getting injured or having an accident	0
Having sex with someone which you later regretted	0
Total number of ARPs reported (among those who had ever consumed alcohol)	**Number of participants reporting this number of problems**
No problems reported	29
One problem reported	4
Two problems reported	6
Three Problems reported	5
Four Problems reported	1
Five problems reported	2

Of the 50 participants who reported having ever consumed alcohol at follow-up, 2 did not complete the item assessing ARPs. For the remaining 48 participants, frequency of ARPs reported is shown in Table 2. For analyses, ARPs were categorised in two ways: a binary categorisation between those who reported no ARPs ($n = 30$) vs. those who reported any ($n = 18$); and, for the purpose of additional exploratory analyses, an ordinal categorisation between those reporting no ARPs ($n = 30$), those reporting 1–2 ARPs ($n = 10$), and those reporting 3–5 ARPs ($n = 8$). When the characteristics of the binary groupings were analysed, those who reported ARPs did not differ from those did not in sex distribution ($\chi^2 = .559$, $p = .454$), age at follow-up ($t(46) = .177$, $p = .860$), SES ($t(45) = -.125$, $p = .901$), age of first alcohol consumption ($U = 176.0$, $p = .287$), or lifetime number of drinking days ($U = 176.0$, $p = .106$). They were, however, more likely to have had a lifetime psychiatric diagnosis at baseline ($\chi^2 = 6.146$, $p = .013$). The 3 ordinal categories also did not differ significantly in sex distribution ($\chi^2 = .571$, $p = .752$), SES ($F(2, 44) = .019$, $p = .981$), or age of first alcohol consumption ($\chi^2(2) = 1.152$, $p = .562$). However, rates of lifetime psychiatric disorder at baseline increased with ARP category ($\chi^2 = 7.390$, $p = .025$), and these groupings also differed significantly in age at follow-up ($F(2, 45) = 3.350$, $p = .044$). Bonferroni post-hoc tests showed that those reporting 3–5 ARPs (mean age at follow-up = 16.9, SD = .3) were significantly older than those

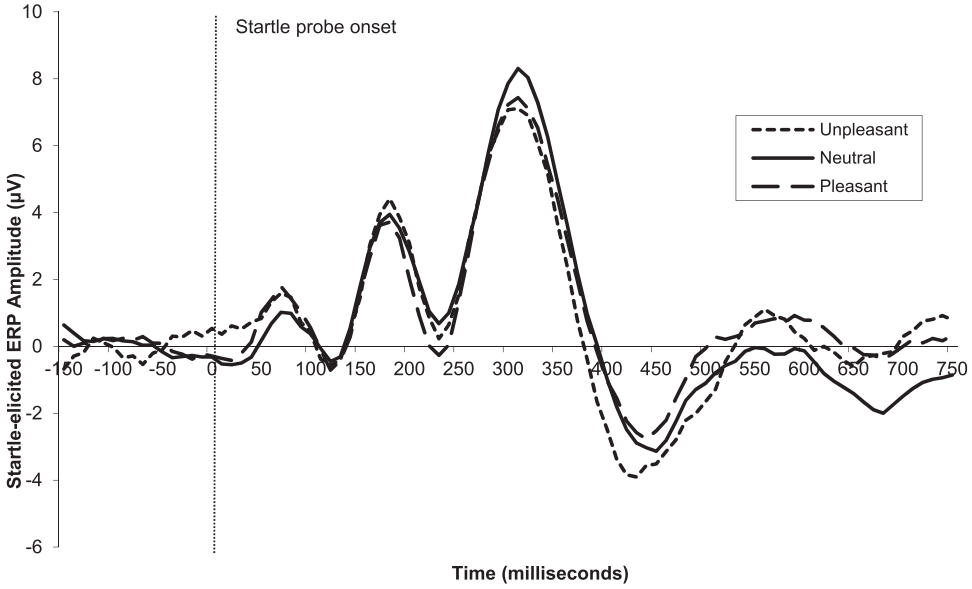

Fig. 1. Grand mean average event-related potential waveform at Pz for neutral, pleasant, and unpleasant pictures.

who reported 1–2 ARPs (mean age at follow-up = 16.3, SD = .4). This was not due to a difference in time between baseline and follow-up ($F(2, 45) = .408$, $p = .668$), but instead a difference in age was also found at baseline ($F(2, 45) = 4.785$, $p = .013$) between the group reporting 3–5 ARPs (mean age at baseline = 13.1, SD = .1) and the group reporting 1–2 ARPs (mean age at baseline = 12.7, SD = .4). Groups also differed in lifetime number of drinking days ($\chi^2(2) = 7.353$, $p = .025$). Post-hoc tests showed that participants reporting 3–5 ARPs reported significantly more lifetime drinking days (median = 40, IQR = 30–50) than participants who reported 1–2 ARPs (median = 19, IQR = 11.5–21.25; $U = 6.0$, $p = .003$) or participants who reported no ARPs (median = 13, IQR = 5–40; $U = 42.5$, $p = .016$), while the latter two groups did not significantly differ ($U(36) = 133.5$, $p = .828$).

Linear regression analyses, controlling for gender, found no significant relationship between P300 amplitude residuals and lifetime number of drinking days (square root transformed), regardless of whether analyses were conducted on the whole sample (P3Pleas: $n = 55$, $R^2 = .002$, $\beta = .010$, $p = .945$; P3Unpleas: $n = 54$, $R^2 < .001$, $\beta = .021$, $p = .881$) or only on those with any lifetime drinking days at follow-up (P3Pleas: $n = 47$, $R^2 = .001$, $\beta = -.005$, $p = .974$; P3Unpleas: $n = 46$, $R^2 = .002$, $\beta = .042$, $p = .785$). Gender was not a significant predictor in any of these linear regression analyses (data not shown). Outcomes of binary logistic regression analyses are shown in Table 3. Lower startle P300 amplitude residuals during pleasant pictures (P3Pleas) significantly predicted higher likelihood of any ARPs. There was a non-significant trend for lower P300 amplitude residuals during unpleasant pictures (P3Unpleas) to also predict ARPs. A scatterplot of standardised P300 amplitude residuals during both pleasant and unpleasant pictures are shown in Fig. 2. No other binary logistic regression analyses approached significance.

Because rates of lifetime psychiatric diagnosis at baseline differed significantly between ARP categories, binary logistic regression analyses of ARPs were repeated with presence lifetime psychiatric diagnosis included, along with gender, as a covariate of P3Pleas or P3Unpleas. Lifetime psychiatric diagnosis was a significant predictor of ARPs in both models. However, P3Pleas remained an independent significant predictor of ARPs (P3Pleas: OR = .795, 95% CI = .652–.970, $p = .024$; lifetime diagnosis: OR = 20.578, 95% CI = 1.483–285.548, $p = .024$). P3Unpleas showed a near-significant trend to predict ARPS when lifetime psychiatric diagnosis was included in the model (P3Unpleas: OR = .867, 95% CI = .751–1.001, $p = .051$; lifetime diagnosis: OR = 13.549, 95% CI = 1.013–181.168, $p = .049$). Gender was not a significant predictor in either model (data not shown).

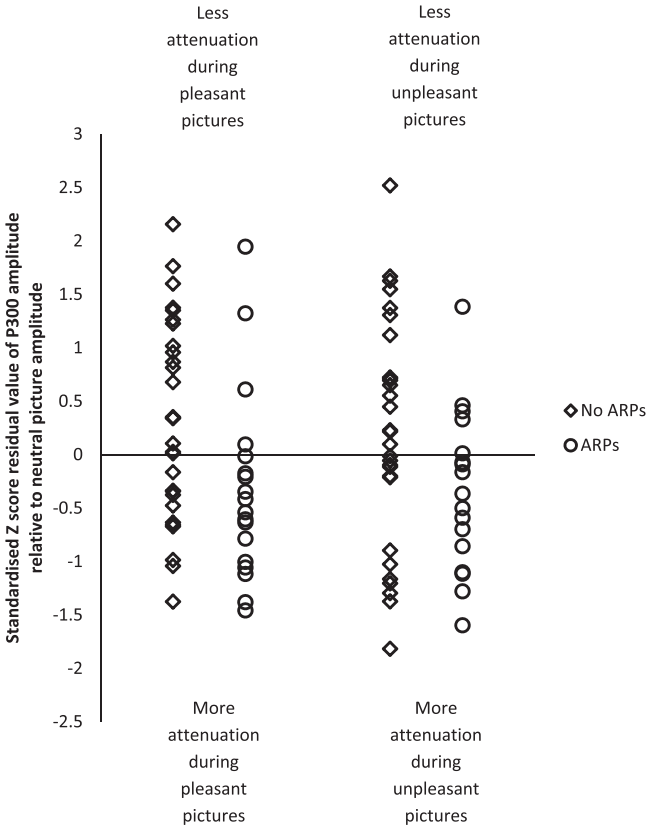

Fig. 2. Scatterplot of standardised residual values for startle-elicited P300 amplitude during pleasant pictures (left) and unpleasant pictures (right). For both picture types, a residual score was calculated for each participant that reflected the amplitude during the affective picture category relative to amplitude during neutral pictures. Relative response scores are plotted separately for participants who reported no alcohol-related problems (diamonds) and those who did report alcohol-related problems (circles).

Table 3
Binary logistic regression results for alcohol outcomes as predicted by P300 amplitude residuals, controlling for gender (N.B., gender was not a significant predictor in any analysis).

Predictor	Outcome (*n* with no missing data)	Odds ratio	95% confidence interval	*p*
Startle P300 during pleasant (relative to neutral) pictures	Any risky drinking in the past month (49)	.983	.860–1.124	.805
	Consumption of any alcohol on ≥ 5 days in the past month (49)	1.058	.907–1.234	.475
	Experience of any alcohol-related problems in the past 12 months (47)	.842	.715–.991	.038*
Startle P300 during unpleasant (relative to neutral) pictures	Any risky drinking in the past month (48)	.965	.858–1.085	.552
	Consumption of any alcohol on ≥ 5 days in the past month (48)	1.105	.956–1.279	.178
	Experience of any alcohol-related problems in the past 12 months (46)	.888	.774–1.020	.093

* $p < 0.05$.

When participants who reported any ARPs were separated into two groups (those who reported 1–2 ARPs and those who reported 3–5 ARPs), ordinal logistic regression analysis showed that P3Pleas significantly predicted ARP category. For a 1 μV increase in P3Pleas, the expected ordered log odds decreased by .149 (95% CI: −.277 to −.021, $p = .023$, $n = 47$) with each move to the next higher category of ARPs. P3Unpleas did not significantly predict ARP category ($p = .117$, $n = 46$). Gender was not a significant predictor of ARP category in either model.

Because rates of lifetime psychiatric diagnosis increased with ARP category and because participants reporting 3–5 ARPs were significantly older than participants reporting 1–2 ARPs, and reported significantly more lifetime drinking days than both other ARP categories, ordinal logistic regression analysis of P3Pleas was repeated with lifetime psychiatric diagnosis, age at follow-up and lifetime alcohol use days (transformed) added to the model as predictors, for the 45 participants who had no missing data for either P3Pleas, number of ARPs, or lifetime drinking days. P3Pleas remained a significant predictor in this model (.225 decrease in expected ordered log odds for a 1 μV increase in P3Pleas with each increase in category; 95% CI: −.405 to −.046, $p = .014$). Lifetime psychiatric diagnosis independently predicted category ($p < .001$) and there was a non-significant trend for increased number of lifetime drinking days to independently predict increased ARPs ($p = .062$). Neither age at follow-up nor gender were significant predictors. A scatter plot of standardised P300 amplitude residuals during pleasant pictures are shown in Fig. 3.

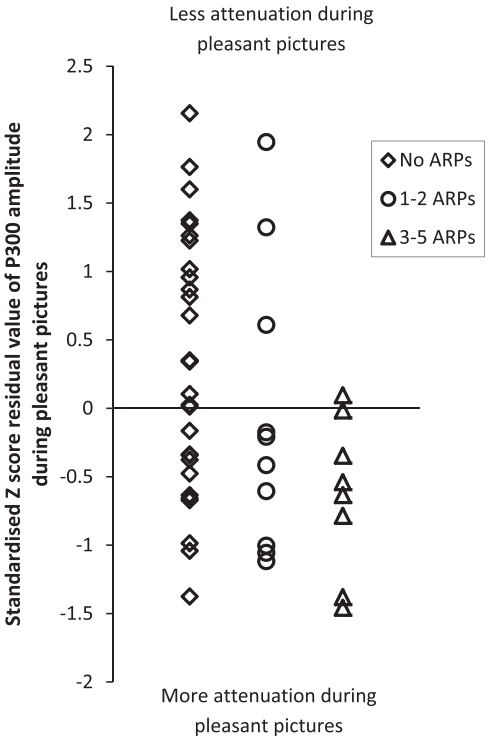

Fig. 3. Scatterplot of standardised residual values for startle-elicited P300 amplitude during pleasant pictures. Relative response scores are plotted separately for participants who reported no alcohol-related problems (diamonds), those who reported 1–2 alcohol-related problems (circles), and those who reported 3–5 alcohol-related problems (triangles).

4. Discussion

The degree to which startle-elicited P300 amplitude was attenuated in 11–13 year olds during viewing of pleasant pictures, relative to amplitude during viewing of neutral pictures, significantly predicted whether or not participants reported alcohol-related problems at follow-up 4 years later. Greater P300 attenuation (i.e. lower P3Pleas) was associated with a significantly greater likelihood of reporting ARPs. Exploratory follow-up analyses that categorised participants based on the number of different ARPs reported suggested that increased P300 attenuation during pleasant pictures predicted higher numbers of ARPs. These findings are consistent with our hypothesis that increased attentional processing of pleasant stimuli would predispose adolescents to high risk drinking. To the extent that those adolescents reporting ARPs represent a population at increased risk of developing alcohol use disorders, our findings support the hypothesis that the reduced responsiveness to pleasant stimuli reported in alcohol-dependent adults (e.g. Heinz et al., 2007) emerges as a consequence of their heavy drinking, rather than preceding it as a predisposing factor.

There was a non-significant trend for larger attenuation of P300 during viewing of unpleasant pictures (i.e., lower P3Unpleas) to predict ARPs. Further investigation in a larger sample would be useful to clarify whether this lack of statistical significance represents a type 2 error due to our small sample size. If so, it would suggest that increased responsiveness to affective stimuli in general, rather than specifically to pleasant stimuli, predisposes adolescents to problematic drinking. This would also be consistent with the strong correlation between P3Pleas and P3Unpleas, which suggests that these two measures may reflect an underlying factor of attentiveness to emotional stimuli in general.

It is of particular interest that the attenuation of P300 amplitude during pleasant pictures did not predict lifetime alcohol use, presence of past-month binge-drinking, or more-than-weekly drinking, but only predicted whether this drinking gave rise to the health, behavioural, and social problems investigated. This suggests either of two possibilities. The first is that increased attentiveness to pleasant stimuli is a risk factor for particularly risky forms of drinking. Adolescents higher in sensitivity to pleasant stimuli may be more sensitive to the "fun" aspects of intoxication (or social activities that tend to lead to intoxication) and therefore be more likely to seek intoxication of a sufficient magnitude to induce ARPs because the anticipated benefits outweigh the anticipated negative consequences, as suggested by Galvan et al. (2007). If this were the case, we would also have expected a relationship between the attenuation of P300 amplitude during pleasant pictures and binge drinking, which was not observed. However, either our time frame (past month) or our definition (5 or more standard drinks) for detection of binge drinking may not have been optimal for detection of the specific drinking patterns that led to the problems reported.

A second possibility is that greater P300 attenuation while viewing pleasant pictures indexes a phenotype more likely to experience ARPs at any level of consumption (i.e. greater sensitivity to alcohol's problematic effects, or greater likelihood of engagement in problematic behaviours while intoxicated). Members of such a phenotype may inadvertently experience ARPs at levels of consumption which do not tend to result in ARPs in peers with lower attenuation during pleasant stimuli. This would explain why this measure predicted ARPs despite not predicting recent frequency of drinking or recent binge drinking. More extensive examination of drinking patterns would be necessary to discriminate between these explanations. It is also particularly interesting that the number of problems reported appeared to be related to the attenuation of P300 amplitude during pleasant pictures. Although the number of times ARPs were experienced was not measured, it is plausible that the number of *types* of problems reported would strongly correlate with the number of problem *events*. This would be consistent with the fact that participants reporting 3–5 ARPs also reported over twice as many lifetime drinking days as other participants, suggesting they had a much greater opportunity to experience multiple separate ARP events. Thus, those reporting higher numbers of ARPs may represent a population who continue to drink in a risky way despite having experienced negative consequences from past risky drinking. They may therefore represent a population at heightened risk of developing an alcohol use disorder. Further longitudinal follow-up could confirm this, though such an investigation would require a larger sample than the one reported here.

These interpretations are subject to several limitations. Data on alcohol use outcomes were based on self-report and thus subject to variations in participants' recall effort, accuracy, and veracity. It is therefore possible that P3Pleas predicted effort to recall, accuracy of recall of, or willingness to divulge ARPs, rather than actual occurrence of ARPs. It is also possible that data for other alcohol use outcomes were mis-categorised due to inaccurate self-report, resulting in failure to detect other existing relationships. Corroboration of self-report with objective data such as records of medical presentations or legal issues arising from alcohol consumption could be used to address this issue in future studies. Self-reported age of first alcohol use was determined at follow-up, and three participants cited ages that were clearly younger than their age at baseline. However, it is possible that several other participants may also have consumed alcohol prior to baseline and, given the lack of assessment of this at baseline, it is unclear to what extent effects may have been confounded by differences between participants in level of alcohol use *preceding* the ERP assessment. However, no participant met criteria for an alcohol use disorder at baseline. Nevertheless, future longitudinal studies would benefit from more comprehensive measures of substance use at all stages of data collection. The proportion of males lost to follow-up (12/38) was significantly larger than the proportion of females lost to follow-up (2/34), and this may have biased results and/or reduced their generalisability.

Finally, the ordinal regression analysis must be treated purely as preliminary and exploratory. Dividing those who reported ARPs into two groups based on the number of ARPs reported resulted in groupings that were smaller (10 reporting 1–2 ARPs and 8 reporting 3–5 ARPs) than what would generally be considered optimal for logistic regression. Nevertheless, it was encouraging that despite low numbers of participants per category, P3Pleas still emerged as a statistically significant predictor, including when variables that differed between those reporting 1–2 ARPs and those reporting 3–5 ARPs (presence of baseline psychiatric diagnosis, age at follow-up, and lifetime drinking days) were entered as covariates. Analyses of response to unpleasant pictures must be treated as exploratory as well, as we did not propose a specific hypothesis regarding its relationship to alcohol outcomes.

In conclusion, increased attentional responsiveness to pleasant stimuli in 11–13 year-olds predicted occurrence of ARPs 4 years later. This provides preliminary support for the use of psychophysiological markers of reward and affective response to index vulnerability to harmful alcohol use. This relationship between reward response and alcohol-related problems may be specific to adolescence, not only because adolescence is the peak period for onset of alcohol use, but also because of the heightened impulsivity and sensation seeking, and incomplete maturation of neural systems associated with behavioural inhibition, during adolescence. Further clarification of this relationship would require studies in larger cohorts, with regard to other addictive substances, over longer follow-up periods, and in different age groups.

Conflict of interest statement

There are no conflicts of interest related to this manuscript.

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