Potentiation of the early visual response to learned danger signals in adults and adolescents

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The reinforcing effects of aversive outcomes on avoidance behaviour are well established. However, their influence on perceptual processes is less well explored, especially during the transition from adolescence to adulthood. Using electroencephalography, we examined whether learning to actively or passively avoid harm can modulate early visual responses in adolescents and adults. The task included two avoidance conditions, active and passive, where two different warning stimuli predicted the imminent, but avoidable, presentation of an aversive tone. To avoid the aversive outcome, participants had to learn to emit an action (active avoidance) for one of the warning stimuli and omit an action for the other (passive avoidance). Both adults and adolescents performed the task with a high degree of accuracy. For both adolescents and adults, increased N170 event-related potential amplitudes were found for both the active and the passive warning stimuli compared with control conditions. Moreover, the potentiation of the N170 to the warning stimuli was stable and long lasting. Developmental differences were also observed; adolescents showed greater potentiation of the N170 component to danger signals. These findings demonstrate, for the first time, that learned danger signals in an instrumental avoidance task can influence early visual sensory processes in both adults and adolescents.

INTRODUCTION

Humans, like other animals, are highly sensitive to signals of danger. In the visual domain, many danger signals are learned rather than innate. This has been demonstrated by work, in both humans and non-human animals, showing that Pavlovian conditioning [which involves associating an initially neutral stimulus, the conditioned stimulus (CS), with a reward or an aversive stimulus] results in learning-dependent potentiation of early sensory responses to the CS in primary sensory areas (Morris *et al.*, 2001; Knight *et al.*, 2004; Weinberger, 2004; Tabbert *et al.*, 2005; Hui *et al.*, 2009; Rosselet *et al.*, 2011).

A similar phenomenon is also observed to discriminative stimuli (S^D) in instrumental tasks, where individuals learn to associate the S^D with a particular response-outcome contingency (Wyrwicka and Sterman, 1968; Recanzone *et al.*, 1992; Recanzone *et al.*, 1993; Weinberger, 1998; Blake *et al.*, 2002). However, no studies to the authors' knowledge have examined the electroencephalography (EEG) indices of these effects. Nor is it established whether there are developmental differences in the modulation of sensory processing in response to Pavlovian and instrumental conditioning during the transition from adolescence to adulthood. Consequently, in this study, we examine whether learning to avoid harm by either emitting (active avoidance) or omitting (passive avoidance) a behavioural response modulates early visual sensory processing, as indexed by an electrophysiological measure that is sensitive to stimulus categories: the N170 event-related potential (ERP).

The N170 is part of the visually evoked N1 components family, which are elicited in response to visual stimuli. The N170 is well known for its face-sensitivity; N170 amplitudes elicited at occipitotemporal electrodes between 140 and 200 ms after stimulus onset are almost always larger in response to faces than in response to non-face objects (Eimer, 2011). However, the N170 is also generated in response to other objects, such as words (Gao *et al.*, 2011; Mercure *et al.*, 2011), and is sensitive to emotional facial expressions (Batty and

Taylor, 2003; Blau *et al.*, 2007; Babiloni *et al.*, 2010; Rellecke *et al.*, 2013). Thus, both non-emotional and emotional learning modulate this component, as seen in learning-dependent changes in N170 amplitude to previously novels objects (Gauthier *et al.*, 1999; Rossion *et al.*, 2002), and during aversive Pavlovian conditioning (Pizzagalli *et al.*, 2003; Dolan *et al.*, 2006).

Dolan *et al.* (2006) used MEG to examine sensory-evoked modulation during differential aversive conditioning with faces. They demonstrated that Pavlovian aversive conditioning was associated with an early modulation that peaked at 150 ms (within the N170 range). This modulation was localized to ventral occipital regions, and reflected a specific emotional learning-dependent enhancement to the visual CS+, which was paired with a loud aversive tone, relative to a control CS−. This study showed that early visual responses to stimuli that predict danger are potentiated when an association is made between an aversive event and a previously neutral stimulus. However, it is currently unknown whether the early visual response is similarly modulated in situations where response contingencies are important. For example, in situations where a warning stimulus (WS) signals indicates an aversive outcome, and the aversive outcome can be avoided by emitting or withholding a behavioural response.

It is also unknown whether similar learning-dependent potentiation to stimuli that predict negative outcomes is found throughout development, specifically during the transition from adolescence to adulthood. Although there is much evidence to suggest that adolescents are highly motivated by rewards (e.g. Steinberg, 2008; Casey *et al.*, 2010; Van Leijenhorst *et al.*, 2010; Ernst *et al.*, 2011), there has not been much work examining the developmental trajectory of Pavlovian and instrumental conditioning to aversive stimuli. Based on a substantial body of work investigating the development of reward processing, it has been argued that the approach system dominates the avoidant system during adolescence, which results in reduced sensitivity to risks in this age group (Ernst *et al.*, 2006, 2009). It has been suggested that reduced sensitivity to risks during adolescence occurs partially as a consequence of weaker associations being made with aversive stimuli (Ernst *et al.*, 2011).

However, adolescence has also been shown to be associated with greater emotional arousal and an increase in the frequency of negative emotions, in comparison to childhood and adulthood (Buchanan et al., 1992; Arnett, 1999; Spear, 2009). Consequently, it is unclear whether the potentiation of early sensory processes to danger signals will be greater or lesser during adolescence. We predict that if there is a deficit in learning aversive outcomes during the transition from adolescence to adulthood, adolescents will show less potentiation of the N170 to danger signals in comparison to adults.

To that end, we used a previously validated avoidance paradigm (Levita et al., 2012) to examine the potential changes in neural activity, specifically in early visual sensory areas, as a consequence of learning to avoid negative outcomes, during the transition from adolescence to adulthood. In this instrumental task, participants were required to learn when to emit and omit a motor response in order to avoid an aversive unconditioned stimulus (US; a loud tone). During the task, participants had to respond to two visually similar warning cues that predicted the onset of the aversive US. One warning cue required participants to emit a motor response to avoid the US (active avoidance), whereas the other cue required participants to inhibit a motor response to avoid the US (passive avoidance). The task also included two other control cues. Participants were told that the control cues did not indicate the imminent presentation of an aversive tone, but that they were nevertheless required to press the response button on the appearance of one cue (control go) and withhold pressing the button on the appearance of the other (control no-go). These cues acted as controls for the warning stimuli, allowing us to examine whether any developmental changes in the N170 component were due to learning-dependent differences in potentiation of early visual responses to danger signals in adolescents and adults, and not a result of developmental differences relating to motor, motor-preparation or visual processes associated with an instrumental procedure.

Avoidance learning is mediated by both Pavlovian and instrumental processes. It has been suggested that in an avoidance paradigm, the WS is initially a Pavlovian excitor, as the organism must first learn the association between the WS and the aversive US, which acquires the capacity to evoke fear via Pavlovian conditioning. Following this, the WS becomes an instrumental discriminative stimulus, signalling that a response will lead to omission of the aversive US (Mowrer, 1951; Rescorla and Wagner, 1972). In addition, it has been shown that fear to the WS declines with training (Herrnstein, 1969; Rachman, 1977). Thus, when the avoidance response has been well learned, avoidance responding persists without much fear being exhibited to the WS (Solomon et al., 1953; Solomon and Wynne, 1954; Mineka, 1979; Lovibond et al., 2008). To investigate the transition in avoidance learning from the WS being a Pavlovian excitor to an instrumental discriminative stimulus, we also examined the amplitude of the N170 in the first and second half of the study. Sustained and elevated N170 amplitude to the warning stimuli throughout the task would indicate that an instrumental discriminative stimulus commands visual attention similar to a Pavlovian stimulus. Alternatively, reduced N170 amplitude in the second half of the task would indicate that potentiation of early visual processing to danger signals is restricted to a Pavlovian excitor.

METHODS
Participants

Twenty-one healthy adolescents aged 12–15 years (mean age 13.14 ± 1.06; 11 females, 10 males) and 23 healthy adults aged 18–32 years (mean age 20.43 ± 3.04; 11 females, 12 males) participated in this study. All participants were right-handed, native English speakers, had normal or corrected-to-normal vision, normal hearing and no known current diagnosis of any neurological or psychiatric condition. Full,

informed consent was received from all participants, as well as from a parent or guardian of adolescent participants. All participants were paid or awarded course credit for their participation. This study was approved by the University of York Ethics Committee.

Adolescent participants were recruited via local advertising around the city of York, England. Parents of interested participants contacted us and completed a screening form to ensure that participants were free from any neurological and psychological conditions and had normal or corrected-to-normal vision. All participants were tested by the same experimenters using the same equipment situated in the same laboratory at the University of York.

Adolescent participants completed the Peterson Pubertal Development Scale to assess their pubertal stage (Petersen et al., 1988; Carskadon and Acebo, 1993). The adolescents in this study had an overall mean pubertal score of 2.15 (s.d. = 0.88). As the maximum score on the Peterson Pubertal Development Scale is 5 (a score indicative of pubertal maturation), adolescents taking part in this study were in the middle of their pubertal development. An independent t-test [$t(15) = 0.013$, $P = 0.99$] revealed that there were no significant differences in puberty scores between the adolescent girls ($M = 2.14$, s.d. = 1.03) and adolescent boys ($M = 2.15$, s.d. = 0.75).

Participants were only included in the data analysis if the number of EEG trials remaining after artefact correction was greater than 30 trials per condition (active avoidance, passive avoidance, control go and control no-go). Due to the number of remaining trials failing to reach criteria, five adults and four adolescents were excluded from the analysis. Consequently, 18 adults (mean age 20.50 ± 3.35; nine males, nine females) and 17 adolescents (mean age 13.06 ± 1.09; eight males, nine females) were included in the behavioural, physiological and EEG analyses.

Stimuli and apparatus

E-Prime Version 1.1 (Psychology Software Tools, Inc., Pittsburgh, PA) was used to construct and deliver the experimental task. Greeble-like were used as the visual stimuli and were created by Scott Yu, provided courtesy of Michael J. Tarr, Center for the Neural Basis of Cognition and Department of Psychology, Carnegie Mellon University (http://www.tarrlab.org/). The experimental task was delivered using an Intel Pentium 4 HT computer, and the visual stimuli were presented in the centre of a 23″ Thin-Film-Transistor (TFT) LCD monitor with a 1920 × 1080 pixel resolution. Participants were seated approximately 60 cm away from the computer monitor used to run the experimental task. A loud aversive sound was used as the US, and consisted of white noise combined with a 1000 Hz tone, which has been shown in previous studies to be aversive (Levita et al., 2009; Soliman et al., 2010). The auditory US was generated using the digital audio editor Audacity 1.2.6 (http://audacity.sourceforge.net), and calibrated using a sound-level meter, microphone, flat-plate adapter and artificial ear, to ensure that the sound did not exceed 95 dB. Sony MSR-XD100 headphones were used to deliver the US during the task.

Experimental task

The task used in this study has been previously validated with adults (Levita et al., 2012), and was designed to examine the neural circuitry engaged in both active and passive avoidance behaviours, where one needs to either emit or omit a motor action in order to avoid a negative outcome (Figure 1). Participants completed three runs of the avoidance task, with each run lasting approximately 6 min. Participants were able to take a short break between each run. Two of the cues presented during the task acted as warning stimuli since they predicted the presentation of an aversive sound (the US, 1 s). The active, passive and control trials were presented in a pseudorandom
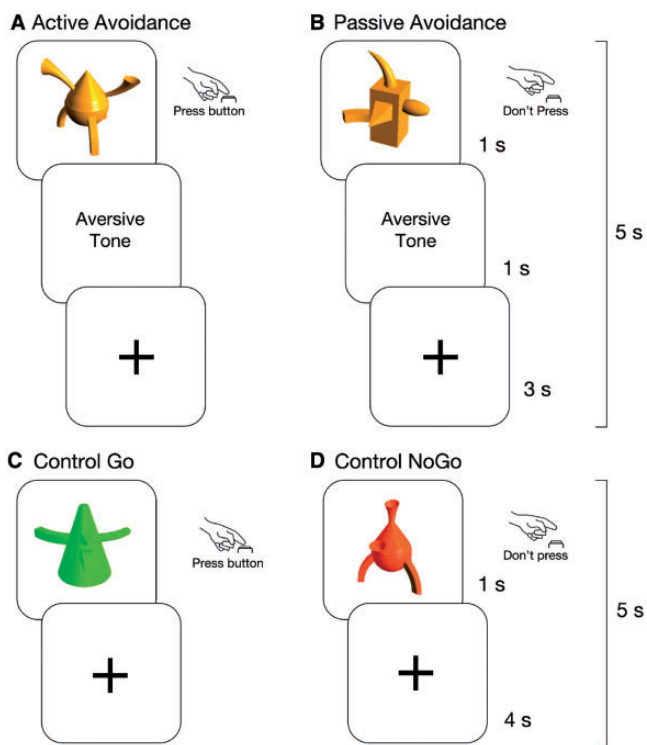
Fig. 1 The experimental task included two warning stimuli (A, B) and two control stimuli (C, D). Each condition was presented 216 times in a pseudorandom order. The warning stimuli predicted the onset of a loud, aversive tone. To avoid the sound, participants had to either press the button (**A**) or not press the button (**B**). Control go and control no-go stimuli acted as controls as they were not paired with an aversive sound. However, they still maintained the same visual and motor components as the warning stimuli. Control go stimuli required participants to press the button (**C**) whereas control no-go stimuli required participants to not press the button (**D**). Participants had to respond while the stimuli were displayed on the screen. Figure adapted from Levita *et al.* (2012).

order, with the same stimulus not being presented more than twice consecutively. In total, there were 72 presentations of each trial type. Participants were told that they could avoid the US (an aversive loud tone) by making a button press while the WS was visible on the screen (1 s). Participants learned that one of the cues required a button press response in order to avoid the aversive US (active avoidance trial, Figure 1A), whereas the other cue required participants to not press the button (omit an action) in order to avoid the aversive US (passive avoidance trial, Figure 1B). The response to the two experimental cues (active or passive avoidance) was counterbalanced between participants. The task also included two control cues. Participants were told that these cues were not associated with an aversive outcome, but were there to ensure that they were paying attention throughout the task. The control go and no-go trials provided comparison conditions to examine emotional-learning-dependent potentiation to the warning stimuli. Additionally, these cues also controlled for potential age-related differences, and hence confounds, in attentional and motor/motor-preparation processes.

Procedure

Before starting the experiment, participants were told that during the task they would be exposed to an aversive loud tone, which they could learn to avoid by either emitting or omitting an action (a button press). Participants were then shown the four visual stimuli they would see during the task. Participants were told that the two yellow stimuli predicted the occurrence of a loud aversive sound, which they could avoid by learning to make the appropriate response. It was explained to participants that one of the yellow characters required a

button press (active avoidance) whereas the other yellow character required them not to press the button (passive avoidance). Participants were told that it was their task to learn what the correct responses were. Participants were also told that the other two stimuli were there to make sure that they were paying attention during the task, and that they should always press the button when seeing the green character (Figure 1C, control go trial) and inhibit a button press response when seeing the red character (Figure 1D, control no-go trial). Participants were explicitly told that the green and red characters were not paired with any outcome, aversive or pleasant, even if their responses were incorrect.

After the instructions had been explained to participants, and before the experimental task began, the EEG cap and the SCR recording electrodes were fitted. On completion of the experimental task, participants were asked to rate the aversive sound they heard by marking a cross on a 100 mm line, which scaled from 'unpleasant' to 'pleasant'. The distance between the unpleasant end of the scale and the participant's cross was measured in millimetres; lower scores reflected that participants found the sound highly aversive. We found that both adolescents ($M = 24.59$, s.d. $= 13.58$) and adults ($M = 22.06$, s.d. $= 9.58$) rated the US to be equally aversive at the end of the task [$t(33) = -0.64$, $P = 0.53$]. Therefore, differences at the electrophysiological level cannot be a result of differences between adolescents and adults in how aversive they found the US. To ensure that participants were aware of the task contingencies, they were asked to recall the correct responses to each WS. No differences in contingency awareness were found between our adolescent and adult participants; all participants were aware of the task contingencies at the end of the study.

Physiological recordings

To examine potential age-dependent differences in emotional arousal levels when avoiding a negative outcome, skin conductance responses (SCR) to the warning and control stimuli were measured during the experiment. SCR was measured using the BIOPAC MP36R system, and analysed using AcqKnowledge 4.1.1. The SCR was sampled at 1000 Hz using disposable electrodermal gel electrodes (BIOPAC, EL507), which were attached to the distal phalanx of the index and middle fingers of the participant's non-dominant hand. Participants were asked to wash their hands with water and dry them gently before the electrodes were attached. The computer running AcqKnowledge and the computer running E-prime were interfaced, allowing generation of digital TTL timestamps for each stimulus so that stimuli presentations during the study were co-registered with the SCR recording. For analysis, the SCR data were resampled at 25 samples/s and a low pass filter of 1 Hz was applied. SCR to the stimuli presentations throughout the experiment were detected using a threshold level of 0.05 μS and a baseline estimation width of 3 s. Importantly, no age-dependent effects in the experienced intensity of the warning stimuli, control stimuli and the US were found during the avoidance task. Therefore, differences at the electrophysiological level cannot be a result of differences between adolescents and adults in how aversive they found the US (see Supplementary Table S1, Supplementary Figure S1 and Supplementary Statistical Analysis).

EEG data collection

Electrocortical activity was recorded using ANT Waveguard 64 channel + GND Ag/AgCl electrode caps, which were fitted according to the 10–20 electrode system. Vertical and horizontal electrooculography electrodes were used to monitor participants' eye movements, allowing for the detection and correction of any ocular artefacts. EEG and electrooculogram (EOG) signals were amplified using an ASA-Lab high-density full-band DC amplifier. EEG had a

sampling rate of 1000 Hz and was recorded continuously. All impedances were kept below 30 Hz. ANT ASA-Lab 4.7 software was used to filter and analyse the EEG signals. Individual data were band-pass filtered at 0.3–30 Hz. A principal components analysis (PCA) was used to identify and remove ocular artefacts, by first identifying eye-blinks on the basis of maximal amplitude deviations of >150 μV on any channel, and then performing a spatial PCA in order to determine the topography of the artefactual signal. Where the PCA procedure identified three or less components, with the components collectively explaining at least 95% of the variance, artefact signals were removed by spatial filtering techniques (Ille *et al.*, 2002). Where the PCA identified a greater number of components, or the components identified did not account for 95% of the variance in the artefactual signal, the data were discarded. On the basis of these criteria, five adults and four adolescents were excluded from the analysis. As participants did not make many errors during the experimental task, all errors trials were recoded and rejected from analyses. Correct trials were split into epochs beginning 0.2 s prior to trial onset until 1.2 s after trial onset. Correct trials were then averaged by shortest event duration.

ERPs analysis

Consistent with existing literature, visual inspection of the grand averaged ERPs revealed a maximal amplitude of the N170 at electrodes P8 and P7 between 130 and 190 ms following stimulus onset. Focusing on these sites also allowed us to characterize the early visual response to our stimulus conditions at both the left and right hemispheres. Thus, all subsequent analyses focused on these two electrode sites. For statistical analyses, peak amplitudes of the N170 were extracted for each participant from each condition (active avoidance, AA; passive avoidance, PA; control go, CG; control no-go, CN) at electrode sites P7 and P8 during the time-window of 130–190 ms post-stimulus onset.

RESULTS

Adolescents and adults show equivalent avoidance behaviour

No significant differences were found between adults and adolescents' acquisition and performance of the task, as measured by the number of errors made in the avoidance conditions (active and passive) and control conditions (control go and control no-go).

As errors rates were non-normally distributed (Shapiro–Wilks), Mann–Whitney tests were conducted to compare the number of errors made for each condition. In both groups, a high and accurate level of performance was observed during all four-task conditions (Figure 2A). There were no significant differences between adults and adolescents in the number of errors made for active avoidance (U = 148.50, Z = −0.15, P = 0.88), passive avoidance (U = 151.50, Z = −0.05, P = 0.96), control go (U = 136.50, Z = −0.56, P = 0.57), or control no-go trials (U = 152.50, Z = −0.02, P = 0.99). However, there were significant differences in the number of errors made during active *vs* passive avoidance trials, whereby both adults (Z = −2.06, P = 0.00) and adolescents (Z = -2.42, P = 0.15) made more errors in the passive avoidance condition, which required them to omit an action to avoid the aversive auditory US.

Analysis of reaction times (RT) in the active avoidance and control go conditions (Figure 2B) revealed that RT to the active avoidance WS did not significantly differ between adults (M = 476.62 ms, s.d. = 52.14) and adolescents (M = 496.05 ms, s.d. = 53.89), t(33) = −1.08, P = 0.29. However, adolescents were slower at responding to the control go stimulus (M = 546.04 ms, s.d. = 48.62) than adults [M = 512.14 ms, s.d. = 45.57, t(33) = −2.13, P = 0.04]. Notably, both adolescents and adults were faster to respond to the WS than the control go cue [adults, t(17) = −3.945, P = 0.001; adolescents, t(16) = −4.801, P = 0.001].
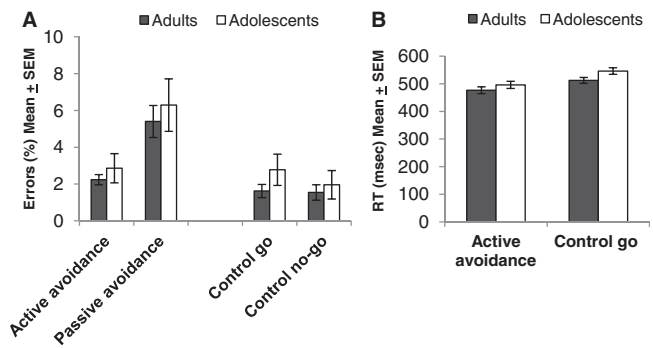

Fig. 2 Task performance. (**A**) No significant differences were found between adults and adolescents' acquisition and performance of the task as measured by the number of errors made in the avoidance conditions (active avoidance and passive avoidance) and control conditions (control go and control no-go). However, both adults and adolescents made more errors in trials where they needed to omit an action to avoid the aversive auditory US. (**B**) Reaction time to the active avoidance warning stimulus did not significantly differ between adults and adolescents. However, adolescents were slower at responding to control go stimulus compared with adults.

N170 peak amplitude

The focus of this study was to examine the effect of danger signals on the potentiation of early sensory processing. Consequently, we examined differences in N170 amplitude in response to the warning and control stimuli in adults and adolescents at two occipitotemporal electrodes, P7 and P8 (Figure 3). To that end, we employed a mixed design analysis of variance with three within-subject factors of Laterality [left hemisphere (P7) *vs* right hemisphere (P8)], Response [Button Press (AA and CG) *vs* No Button Press (PA and CN)], Danger [Avoid (AA and PA) *vs* Control (CG and CN)], and a between-subject factor of Group (Adults *vs* Adolescents). For mean values and standard deviations of the N170 in P7 and P8, see Supplementary Table S2 and Supplementary Figure S2.

This analysis revealed a significant main effect of Danger; N170 amplitudes in response to the warning stimuli were increased in comparison to the control stimuli [Danger, $F(1,33) = 106.19$, $P = 0.001$, $h_p^2 = 0.763$]. Since there was no significant effect of Response [$F(1,33) = 0.793$, $P = 0.396$, $h_p^2 = 0.022$], and no interaction of Danger × Response [$F(1,33) = 0.512$, $P = 0.479$, $h_p^2 = 0.015$], the main effect of Danger indicates an enhanced N170 to danger signals that is unaffected by the response contingencies implied by those signals, which were either emitting or omitting an action to avoid the negative outcome.

There was also a significant main effect of Group; N170 amplitude was greater overall in adults than in adolescents [Group, $F(1,33) = 9.265$, $P = 0.005$, $h_p^2 = 0.219$]. A significant Danger × Group interaction was also found [$F(1,33) = 8.362$, $P = 0.007$, $h_p^2 = 0.202$]. These findings reveal a developmental difference between adults and adolescents, whereby the potentiation of the N170 by warning stimuli was greater in adolescents than in adults.

Finally, there was a significant Laterality × Danger interaction [$F(1,33) = 15.728$, $P = 0.001$, $h_p^2 = 0.323$], showing that the enhancement of the N170 to Danger was greater in the right hemisphere (P8) than in the left hemisphere (P7). Other main effects and interactions were non-significant ($P > 0.05$).

Learning-dependent modulation of the N170 over the course of training

Our experimental design also allowed us to examine the amplitude of the N170 in the first and second half of the study (the first 36 trials versus the last 36 trials for each condition). This comparison allowed us to examine whether the N170 changes as the WS transitions from

A Adults
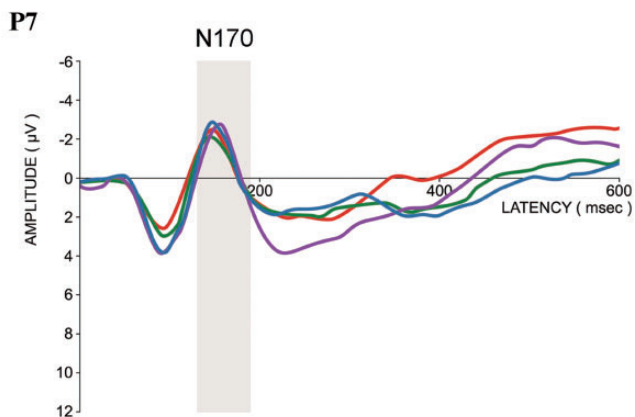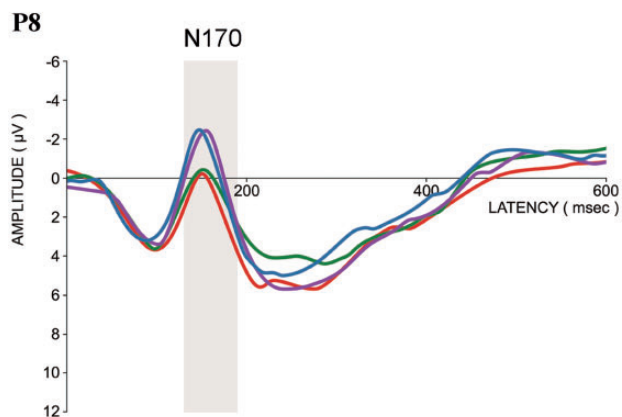
B Adolescents
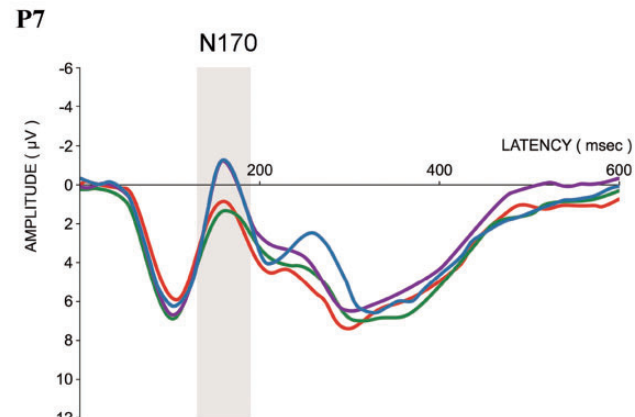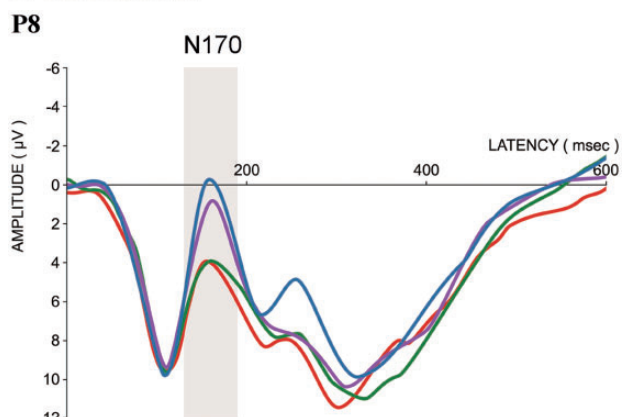
Blue = Active avoidance; Purple = Passive avoidance; Green = Control go; Red = Control no-go

Fig. 3 Grand-average ERP responses as a function of condition (active avoidance, passive avoidance, control go, control no-go) at electrode sites P8 and P7 for (**A**) adults and (**B**) adolescents. Blue, active avoidance; purple, passive avoidance; green, control go; red, control no-go.

being a Pavlovian fear CS to an instrumental discriminative stimulus during the task. Elevated N170 responses to the warning stimuli throughout the task would indicate that an instrumental discriminative stimulus commands visual attention just like a Pavlovian stimulus. Alternatively, smaller N170 responses at the end of the task would indicate that enhanced visual processing is restricted to a Pavlovian excitor, which would only be seen when the aversive stimulus is expected.

This analysis revealed a significant main effect of Time [$F(1,34) = 93.062$, $P = 0.001$, $h_p^2 = 0.732$], showing that N170 amplitudes in the first half of the experiment were larger than those in the second half of the experiment. Notably however, there was no significant Time × Danger interaction [$F(1,34) = 0.420$, $P = 0.522$, $h_p^2 = 0.012$]. This pattern of results shows that the modulation of N170 by the warning stimuli is augmented throughout the study as N170 amplitudes in the second half of the experiment were decreased on both Danger and Control trials to a similar degree (Figure 4). This pattern of results is consistent with general habituation/fatigue effects, rather than a reduction in the potency of the warning signal in eliciting an enhanced N170 amplitude.

Scalp topography of the N170

Voltage maps showing the scalp topography of the differences in N170 amplitude between the two avoid conditions and their respective
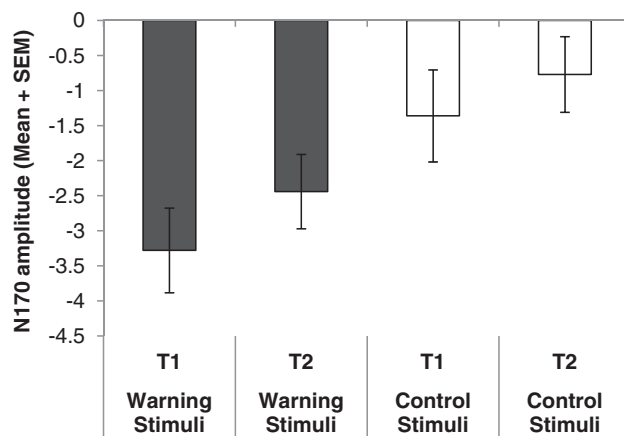

Fig. 4 Enhancement of N170 amplitude to the warning stimuli compared with the control stimuli in adults and adolescents during the first half (T1) and second half of the study (T2).

control conditions are illustrated in Figure 5. The scalp topography is consistent with findings reported in the N170 literature, with the maximal negativity being observed at lateral posterior electrode sites, and a corresponding positivity at the apex. Although a source analysis of the generators of the N170 is beyond the scope of this study, the
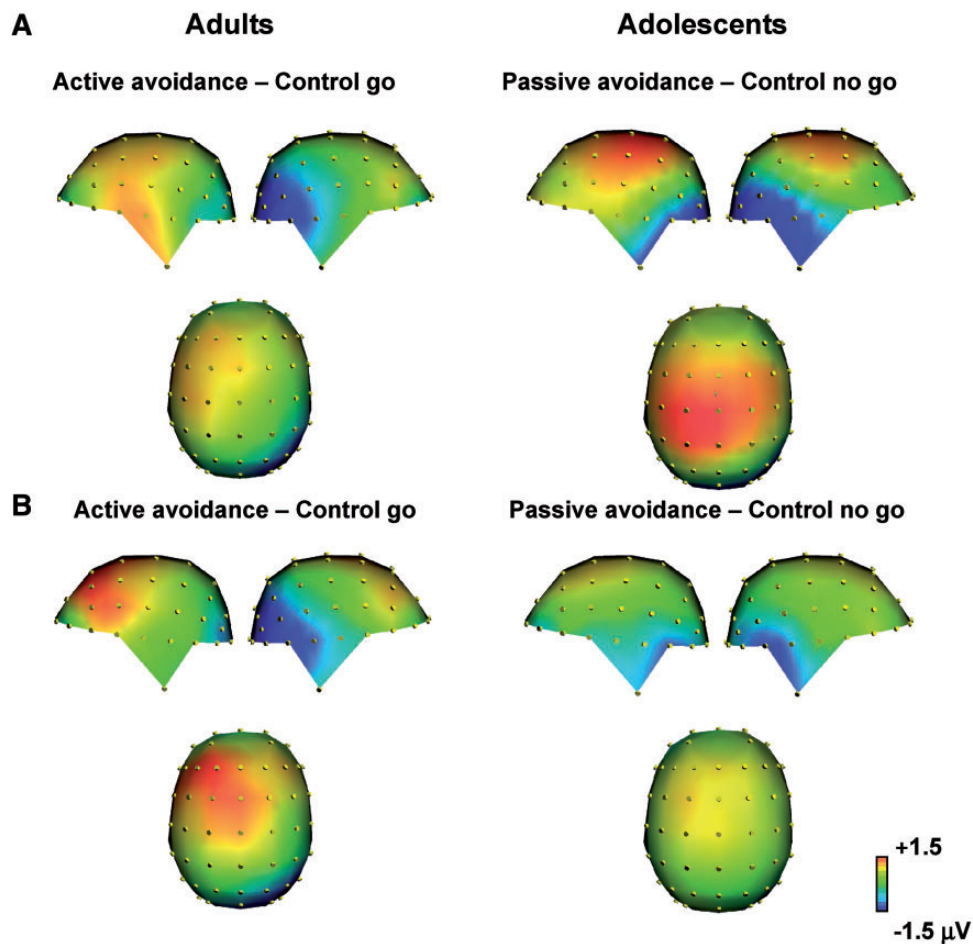
Fig. 5 Topographical maps showing voltage differences (at 160 ms) between (**A**) active avoidance minus control go conditions and (**B**) passive avoidance minus control no-go conditions for adults (column 1) and adolescents (column 2).

similarity of the scalp topography reported here with the findings generally reported in the literature strongly suggests that the modulation of the N170 reported here is consistent with an increased response of the primary generators of the N170 component, rather than reflecting the actions of additionally recruited brain regions.

DISCUSSION

In this study, we found that learned danger signals are associated with the potentiation of early visual sensory processes. This phenomenon is of fundamental importance as survival and adaptive behaviour rely on rapid detection and response to stimuli that predict potential future harm. We found that learning to avoid a negative outcome, by either emitting an action or withholding an action, was associated with greater learning-dependent potentiation of the N170 component evoked by the warning stimuli, but not by the control stimuli, as measured by the N170 component over the occipitotemporal electrodes P7 and P8. In addition, the augmentation of the N170 by the warning stimuli was maintained throughout the avoidance task, despite overall habituation of the N170 response. Finally, we found that adolescents had greater potentiation of the N170 to the warning stimuli than that of adults, demonstrating a developmental difference in N170 potentiation to danger signals.

Learning-dependent potentiation of the N170

This study demonstrates that early visual responses are modulated in situations where response contingencies are important. For instance, in

circumstances where a warning signal can predict an aversive outcome, and when that aversive outcome can be avoided by emitting or withholding a behavioural response. Under these conditions, we found that the potentiation of the N170 to danger signals was independent of the required operant response, which involved either emitting (active avoidance) or withholding (passive avoidance) an action to avoid harm. This was demonstrated by our finding that in both adults and adolescents the enhancement of the N170 component was equal in magnitude to both avoidance warning stimuli, despite the two stimuli requiring two very different responses to avoid harm.

The visual cues used as the warning and control stimuli in our experimental task were greebles-like. In line with our findings, greebles have previously been shown to evoke the N170 component in occipitotemporal locations (Gauthier *et al.*, 1999; Carmel and Bentin, 2002; Rossion *et al.*, 2002; Bentin *et al.*, 2007). Notably, greebles have features that are face-like in terms of their overall configuration and symmetry (Xu *et al.*, 2005), and the N170 has been reliably associated with face processing (Eimer, 2011). Hence, these features could be driving the N170 response in our study. However, it has also been shown that the N170 is also evoked in response to other classes of stimuli (Gao *et al.*, 2011; Mercure *et al.*, 2011) and is modulated by unconditioned emotional stimuli, such as happy or fearful faces (Blau *et al.*, 2007; Krombholz *et al.*, 2007; Montalan *et al.*, 2008; but see, Rellecke *et al.*, 2013) and naked bodies (Hietanen and Nummenmaa, 2011). Irrespective of whether the face-like features of the greebles evoked the N170 component, we found that the potentiation of the

N170 was only observed in response to the warning stimuli, and not the control stimuli.

Models of avoidance behaviour stress the role of both Pavlovian and instrumental processes in learning to avoid negative outcomes. The highly influential two-factor theory of avoidance learning (Mowrer, 1951), and newer models of avoidance behaviour that address the weaknesses in Mower's original theory, emphasis the involvement of both Pavlovian and operant components in avoidance behaviour (Declercq et al., 2008; Lovibond et al., 2008). Our electrophysiological data suggest that the effects we observed were not restricted to the early learning component. We found that the potentiated N170 response to the warning stimuli remained high throughout the experiment in both adults and adolescents. This suggests that an instrumental discriminative stimulus commands visual attention just like a Pavlovian stimulus.

Early on in an avoidance paradigm, the WS is primarily a Pavlovian excitor as the organism must first learn the association between the WS and the aversive US. Later on in training, the WS becomes an instrumental discriminative stimulus, signalling that a response will lead to omission of the aversive US (Mowrer, 1951; Rescorla and Wagner, 1972), and fear to the WS subsides (e.g. Solomon et al., 1953; Solomon and Wynne, 1954; Mineka, 1979; Lovibond et al., 2008). The issue of what maintains avoidance responses is an important one, and we had hoped that examining emotional reactivity as indexed by the SCR in this paradigm would provide a measure to assess changes in fear (as evoked by the warning stimuli) over training. However, the lack of clear dissociation between the SCR to the avoidance or control cues made it hard to know whether the reduction in SCR reflected a specific reduction in the fear response to the warning stimuli over the course of training.

The maintenance of the potentiation of the N170 over time is consistent with the idea that an instrumental discriminative stimulus commands visual attention in a similar way to a Pavlovian CS, as demonstrated by earlier studies that found learning-dependent enhancements in sensory responses to conditioned stimuli in purely Pavlovian tasks (Weinberger et al., 1993; Thiel et al., 2002; Pizzagalli et al., 2003; Dolan et al., 2006). For instance, Pizzagalli et al. (2003) administered a Pavlovian fear-conditioning paradigm to adults and reported an ERP component, which was predominantly right-lateralized to lateral occipitotemporal regions and showed relatively stronger current density to a CS predicting an aversive noise than to a neutral stimulus. The right side potentiation effect observed by Pozzagalli et al. (2003) was also observed in this study in both adolescent and adult participants. This finding is consistent with previous work on facial processing, showing that facial emotions potentiate the N170 and generally produce greater right hemisphere activity (Williams et al., 2006). This finding is also in line with a large body of work suggesting that the right hemisphere is more involved in processing emotional stimuli (Adolphs, 2002). Furthermore, electrophysiological and neuroimaging studies often show a preferential involvement of right sided activity within the first 200 ms of processing emotional stimuli (Pizzagalli et al., 1999, 2002; Streit et al., 2000; Kawasaki et al., 2001).

A key aim of this study was to examine whether there were any age-dependent effects in emotion-dependent potentiation of early sensory percepts. To date, there is substantial evidence in support of the view that adolescents are highly motivated by rewards (e.g. Steinberg, 2008; Casey et al., 2010; Van Leijenhorst et al., 2010; Ernst et al., 2011). However, there are inconsistencies in the literature regarding adolescent responses to negative outcomes, with some studies supporting the attenuation of adolescent sensitivity to aversive stimuli, and others supporting a potentiation (for review, see Spear, 2011). Some of the uncertainty surrounding this issue stems from the majority of previous studies examining avoidance learning in adolescents without an adult comparison group (Liberman et al., 2006; Lau and Viding, 2007;

Schlund et al., 2010). Moreover, these studies often use different types of aversive stimuli for adults and adolescents and thus developmental differences cannot be directly assessed (Ernst et al., 2011). For example, some studies have used an aversive tone for child and adolescent participants (Liberman et al., 2006; Neumann et al., 2008), and electric shocks for adult participants (e.g. Delgado et al., 2009).

In order to avoid this confound, adult and adolescent participants in this study completed the same avoidance paradigm, which required them to learn when to emit and omit a motor response to avoid hearing a loud aversive tone. This approach allowed us to directly compare adults and adolescents' behavioural performance. We found that adolescents completed the task as quickly and as accurately as adults. Furthermore, both groups rated the US as equally aversive and learned to avoid the negative outcome equally well. Nevertheless, the learning-dependent potentiation of the response of posterior perceptual regions to danger signals was greater in adolescents than in adults. This developmental effect was not a result of performance or emotional arousal differences between the two groups, as both adults and adolescents learned and performed the task equally well, and found the US, a loud tone, to be equally aversive. Hence, within the context of this study, these data do not support the suggestion that during adolescence weaker associations are being made with aversive stimuli (Ernst et al., 2011), and that adolescents have reduced harm perception compared with adults (Ernst et al., 2006).

Neurophysiological models of learning-dependent potentiation of the N170

In this study, we show learning-dependent potentiation of the N170 to warning stimuli. However, the neurophysiological mechanisms that underlie the potentiation of early sensory percepts to danger signals in humans are currently unknown. In adults it has been shown that the potentiation of auditory percepts, in both rodent and human auditory cortices, is mediated by acetylcholine (Thiel et al., 2002; Weinberger, 2004). However, it is unknown whether the cholinergic system plays a similar role in the potentiation of visual sensory processes. This is an important empirical question that needs to be investigated in future work.

Nonetheless, there is evidence to suggest that the potentiation of visual components in adults, as a result of learning about negative outcomes, is a consequence of direct and indirect reentrant influences from the amygdala to visual pathways that serve to enhance perception to sensory events of value (Dolan, 2002; Vuilleumier, 2005). It is thought that these direct and indirect loops are the mechanism by which stimuli that signal danger can capture subjects' attention. This leads to a more efficient detection of, and faster responses to, threatening situations (Armony and Dolan, 2002; Carlson and Reinke, 2010) and action-selection mechanisms that help maximize the organism's ability to avoid harm (Williams, 2006).

This idea is consistent with the anatomical connectivity between the visual system and the amygdala (Pessoa and Adolphs, 2010). There is strong evidence to suggest that visual emotional discrimination processes are mediated by reentrant feedback from the amygdala to ventral visual cortex. Moreover, identifying the emotional relevance of stimuli is thought to originate during the interaction between rostral ventral visual cortex and amygdala (Amaral et al., 2003; Freese and Amaral, 2005, 2006; Sabatinelli et al., 2009). The way in which interactions between the amygdala and visual areas lead to both short- and long-term plastic changes that mediate learning-dependent potentiation of early sensory percepts also needs to be further investigated. In this study we examined short-term plastic changes in the response of early visual areas to warning stimuli, and future work needs to examine the long-term stability of this phenomenon.

The brain imaging methodology used in this study, EEG, precludes the ability to directly examine the putative interactions between the amygdala and visual areas in relation to our findings. Interestingly, however, it has been shown that during adolescence amygdala activation to emotional stimuli is greater than during childhood or adulthood (Hare *et al.*, 2008). If amygdala responses are enhanced during this developmental period, it would feed forward to the reentrant feedback from the amygdala to ventral visual cortex, which could potentially explain the greater potentiation of the N170 to the warning stimuli in this age group.

Conclusion

In both adults and adolescents, greater N170 ERP amplitudes were found to both the active and passive avoidance stimuli. Moreover, we found that the potentiated N170 response to the warning stimuli remained high throughout the experiment, which suggests that an instrumental discriminative stimulus commands visual attention just like a Pavlovian stimulus. Finally, developmental differences were observed; adolescents showed greater potentiation of the N170 component to danger signals. Adolescence is a developmental period characterized by intense emotional experiences and behaviours (Spear, 2009; Steinberg, 2007). Our findings suggest that these emotional experiences and behaviours may not be solely the result of a functional and structural disparity between the maturity of the prefrontal cortex and subcortical regions (e.g. Ernst *et al.*, 2006; Ernst and Fudge, 2009; Somerville *et al.*, 2010). Instead, they suggest that the development of cognitive and emotional control throughout adolescence is a result of a continued maturation process involved in the integration of more widely distributed neural circuitries (Luna, 2009), which include posterior temporal regions involved in processes that potentiate our responses to danger signals. This is supported by the greater difference in responsivity to danger signals than control stimuli in adolescents compared with adults, which could provide, at least partially, a neurobiological explanation as to why adolescents often show greater emotional arousal, and experience more frequent negative emotions than children and adults (Buchanan *et al.*, 1992; Arnett, 1999; Petrides and Pandya, 1999; Spear, 2009).

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

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