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Differential fear conditioning in Asperger's syndrome: Implications for an amygdala theory of autism

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Abstract

Since the first descriptions of individuals with autism spectrum disorders (ASD), abnormalities in socio-emotional behaviours have been described as amongst the most characteristic clinical features of this condition. Current evidence in this area suggests that individuals with ASD experience difficulties in the perception and expression of emotions within the social domain. The causes for these emotional difficulties are, however, still poorly understood. At the developmental level, it is unclear whether emotional disturbances constitute a primary feature of the clinical presentation of ASD or whether they are secondary to abnormalities in other areas of cognition. At the neurobiological level, it is still debated to what extent abnormalities of the limbic system, in particular the amygdala, may be responsible for the emotional disturbances characterising ASD. Here we show that a group of individuals with Asperger's syndrome exhibit a pattern of abnormality in differentially acquiring fear, which suggests that their fear responses are atypically modulated by conditioned and non-conditioned stimuli. On the basis of these results and the existing literature we suggest that ASD may be characterised by atypicalities in the integration of physiological and cognitive aspects of emotional experiences which we argue arise because of poor connectivity between the amygdala and functionally associated cortical areas.

Keywords: Autism Spectrum Disorder; cortico-amygdala connectivity; emotional processes; psychophysiological reactivity.

Abbreviations: ASD = autism spectrum disorder; CS = conditioned stimulus; UCS = unconditioned stimulus; CR = conditioned response; UCR = unconditioned response; SCR = skin conductance response.

Fear Conditioning in Asperger's syndrome: Implications for an amygdala theory of autism

1. Introduction

Autism is a developmental disorder mainly characterised by impairments in reciprocal social and emotional behaviours accompanied by varying degrees of abnormal cognitive development. Although autistic disorder is distinguished from Asperger's syndrome (World Health Organisation, 1992; American Psychiatric Association, 2000) on the basis of language development, which is significantly delayed in the former but not the latter, it is now widely accepted that both conditions form part of the same spectrum of syndromes. Research over the past half a century has provided a rather detailed description of the extent and nature of the social and cognitive difficulties experienced by individuals with autism spectrum disorders (ASD), but despite Kanner's (1943) emphasis on the role of abnormal affect in the clinical manifestations of autism, the study of emotional processes in ASD is relatively limited.

In the current paper we draw on the fear conditioning literature in order to provide further insights into emotional processes in ASD. Fear conditioning is a form of Pavlovian conditioning through which individuals learn the hedonic values of previously neutral stimuli via a process of association. In a typical fear conditioning study participants are presented with a simple visual or auditory stimulus alongside a painful or noxious stimulus such as a startling noise or mild electric shock (the unconditioned stimulus; UCS). Naturally, individuals will respond to such noxious stimuli with species-typical defence behaviours (the unconditioned response; UCR) such as increased autonomic activity, which in humans can readily be measured by monitoring skin conductance responses (SCR; Frederikson, Annas, Georgiades, Hursti & Tersman, 1993). After a few pairings of the neutral stimulus and the UCS, participants will start to exhibit such fear responses to the neutral stimulus alone (the stimulus has become a conditioned stimulus; CS), indicating that they have learned the association between the noxious and neutral stimuli.

To date, only one investigation has examined fear conditioning in ASD. Bernier and colleagues (Bernier, Dawson, Panagiotides & Webb, 2005) employed a potentiated startle paradigm in order to assess simple fear conditioning in a group of adolescents and adults with ASD. The authors

aversively conditioned participants to a red square by pairing its presentation with an aversive puff of air to the throat. Following several pairings of the red square and the puff of air, the authors assessed participants' eye-blink startle response to either a loud noise presented alone or accompanied by the red square. The results showed that as in typical participants, eye-blink startle responses in the ASD group were enhanced during the trials including the red square indicating that both groups had learned the aversive nature of the conditioned stimulus to similar extents.

There are several reasons why such studies of fear conditioning are of value to our understanding of ASD. First, as Bernier and colleagues point out, such studies contribute to our understanding of the neuropathology underlying this spectrum of disorders. Extensive animal (see LeDoux, 1994, 1995, 1998, 2000 for detailed reviews) and human (Bechara, Tranel, Damasio, Adolphs, Rockland & Damasio, 1995; Büchel, Morris, Dolan & Friston, 1998; Büchel, Dolan, Armony & Friston, 1999; Cheng, Knight, Stein & Smith, 2003; Knight, Smith, Cheng & Stein, 2004; LaBar, LeDoux, Spencer & Phelps, 1995; LaBar, Gatenby, Gore, LeDoux & Phelps, 1998; Morris, Őhman & Dolan, 1997; Morris, Friston & Dolan, 1997, Morris, Friston & Dolan, 1998; Phelps, LaBar, Anderson, O'Connor, Fulbright & Spencer, 1998) research has demonstrated that the associative learning in fear conditioning paradigms is mediated by the amygdala, a limbic structure which has attracted increasing attention in relation to ASD in recent years. Although several lines of research have implicated the amygdala in the pathology underlying this disorder (e.g. Bachevallier, 1994; Bachevallier, 2000; Baron-Cohen et al., 1999; Baron-Cohen, Ring, Bullmore, Wheelwright, Ashwin, & Williams, 2000; Fotheringham, 1991; Howard, et al., 2000; Sweeten, Posey, Shekhar & McDougle, 2002), the evidence is somewhat inconsistent and the extent and nature of the proposed amygdala pathology remain unclear (see Sweeten et al., 2002; Amaral, Bauman & Mills Schumann, 2003; Palmen, van Engeland, Hof & Schmitz, 2004 for recent reviews). Fear conditioning paradigms are valuable in this respect because different forms of conditioned fear behaviour have been shown to rely on different amygdala nuclei or pathways. The acquisition of fear in simple conditioning paradigms such as the one employed by Bernier and colleagues (2005), for example, is thought to be mediated primarily by a sub-cortical amygdala system involving direct sensory afferent projections from thalamic nuclei and efferent connections to various brainstem and hypothalamic nuclei that mediate the behavioural and physiological fear responses (LeDoux, 1998; LeDoux, 2000). As Bernier and colleagues (2005) point out, their findings suggest that at least this sub-cortical system appears to be functionally relatively

intact in ASD. Important for our current investigation are findings which suggest that fear acquisition in more complex differential fear conditioning paradigms, in which participants acquire fear to only one of several different stimuli (e.g. different colours), have been shown to rely on cortical modulation of the sub-cortical amygdala system (Jarrell, Gentile, Romanski, McCabe & Schneiderman 1987; Morris et al., 1997). This cortical modulation is thought to be important for the regulation of fear responses according to the specific conditioning contingencies (i.e. responding to the conditioned stimulus but not to the non-conditioned stimuli). Since several lines of evidence indicate that ASD may be characterised by poor connectivity between disparate brain regions (Belmonte, Allen, Beckel-Mitchener, Boulanger, Carper & Webb, 2004; Ben Shalom, 2000; Brock, Brown, Boucher & Rippon, 2002; Castelli, Frith, Happe & Frith, 2002; Just, Cherkassky, Keller & Minshew, 2004; Just, Cherkassky, Keller, Kana & Minshew, in press; McAlonan, et al., 2005; Rippon, Brock, Brown & Boucher, in press), an investigation of differential fear conditioning in ASD may provide valuable behavioural insights into the functional integrity of cortico-amygdala connectivity in this population.

In addition to providing further insights into the functional integrity of amygdala systems, studies of fear conditioning may also inform debates about the developmental role of emotional atypicalities in the clinical presentation of ASD. To date most investigations relevant to this debate have focused on how individuals with ASD perceive and express emotions within the broader context of social behaviour. Although the evidence in this area is relatively consistent in illustrating that ASD is characterised by difficulties in the recognition (Hobson, 1986a,b; Hobson, Ouston & Lee, 1988a,b; Hobson, 1991; Weeks & Hobson, 1987) and context appropriate expression of emotions (Dawson, Hill, Spencer, Galpert & Watson, 1990; Kasari, Sigman, Mundy & Yirmiya, 1990; Kasari, Sigman, Baumgartner & Stipek, 1993; Sigman, Kasari, Jung-Hye & Yirmiya 1992; Yirmiya, Kasari, Sigman & Mundy, 1989; Yirmiya, Sigman, Kasari & Mundy, 1992), these findings can be accommodated within competing explanatory frameworks. In line with Kanner's (1943) original conclusion, some authors have argued that emotional atypicalities constitute a primary and possibly innate feature of the autistic phenotype. Hobson (1989) for example suggests that individuals with ASD are characterised by difficulties in understanding the hedonic value of their sensory-motor environment which results in an abnormal developmental progression of interpersonal relatedness (See Mundy & Sigman, 1989 for a similar suggestion). Others, however, argue that the emotional difficulties evident in ASD are secondary to impairments in more general socio-cognitive processes. Schultz (2005), for example,

argues that primary face processing atypicalities are responsible for the aberrant development of socio-emotional behaviours, whilst Baron-Cohen and colleagues (Baron-Cohen et al., 1999, Baron-Cohen et al., 2000) have suggested that difficulties in Theory of Mind (ToM) understanding give rise to the abnormal social and emotional behaviours characterising the autism spectrum. These latter accounts are supported by evidence which suggests that individuals across the autism spectrum experience difficulties in processing faces (e.g. Gross, 2005; Joseph and Tanaka, 2003; Partland, Dawson, Webb, Panagiotides & Carver, 2004; Spezio, Adolphs, Hurley & Piven, in press) and understanding mental states such as beliefs and desires of others (e.g. Baron-Cohen, Leslie & Frith, 1985; Happe, 1995; but see Bowler, Briskman, Gurvidi & Fornells-Ambrojo, 2005). Fear conditioning paradigms may provide important new insights into this issue because they assess a relatively basic and automatic emotional process that does not necessitate intact socio-cognitive processes. In addition, because fear conditioning paradigms assess the processes by which individuals learn the hedonic value of sensory stimuli, such paradigms constitute a relatively direct test of Hobson's (1989) suggestion that ASD may be characterised by atypicalities in understanding the hedonic value of their sensory-motor environment.

Finally, studies of fear conditioning in ASD will add to a small but growing number of studies that have investigated emotional processes in this population at the psychophysiological rather than the behavioural level. Since it is widely accepted that psychophysiological responses form an integral part of emotional experiences and behaviours (Cannon, 1929; James, 1884), the investigation of such responses in ASD is vital to understanding the nature of emotional atypicalities in this population. The limited evidence in this area to date suggests that like typical individuals, individuals with ASD exhibit changes in autonomic activity, such as increases in skin conductance responses (SCR) or changes in heart rate, when presented with emotionally salient pictures (Ben Shalom et al., 2003; Blair, 1999; Hillier, Carpenter, Smith, Berntson & Beversdorf, 2006; Salmond, de Haan, Friston, Gadian & Vargha-Khadem, 2003), aversive auditory stimuli (Bernier, Dawson, Panagiotides & Webb, 2005; Salmond et al., 2003) or emotive words (Gaigg & Bowler, 2006). However, these physiological responses seem to be atypically modulated by specific stimulus properties in ASD. Blair (1999) for example found that although children with ASD exhibited typically increased SCRs to distress cues (e.g. crying face) as compared to neutral images, their responses to threatening images (e.g. gun) were less consistently elevated than in the comparison group (see Hillier et al., 2006 for similar findings).

Similarly, SCRs to faces in ASD have been found to be abnormally modulated by the direction of gaze (Joseph, Ehrman, McNally & Tager-Flusberg, 2005; Kylliainen & Hietanen, 2006). As Ben Shalom (2000) suggests, this pattern of results would be in line with the suggestion that ASD is characterised by atypicalities in the connectivity between cortical areas responsible for the cognitive appraisal of emotional stimuli and the amygdala which mediates our physiological reactions to such stimuli. Such a view is also supported by the finding that unlike in typical individuals, SCRs do not seem to correlate with subjective ratings of emotionality in ASD (Gaigg & Bowler, 2006; Hillier et al., 2006).

As this brief overview of the literature illustrates, there are several reasons why the study of fear conditioning is important for our understanding of ASD. In the current study we draw on a differential fear conditioning paradigm employed by Bechara and colleagues (Bechara et al., 1995) in order to test the hypothesis that individuals with ASD would exhibit a pattern of atypicality consistent with the suggestion that the amygdala is abnormally modulated by cortical areas. Thus, on the basis of the evidence suggesting that the sub-cortical amygdala system is functionally intact in ASD (e.g. Bernier et al., 2005) we hypothesised that a group of ASD participants would exhibit typical patterns of physiological responses to aversive stimuli and that their autonomic activity would exhibit evidence of learning the hedonic value of a previously neutral stimulus. However, based on the suggestion that the amygdala may not be modulated normally by cortical areas, we expected that participants with ASD would not exhibit a typical pattern of acquiring fear discriminately to conditioned and non-conditioned stimuli. If our predictions are borne out this pattern of results would lend support to Hobsons' (1989) suggestion that ASD may be characterised by difficulties in understanding (in this case learning about) the hedonic value of their sensory-motor environment.

2. Method

2.1. Participants

Fifteen individuals with Asperger's syndrome (12 male, 3 female) and sixteen typical individuals (13 male, 3 female) participated in this experiment. One female Asperger and two male comparison participants were excluded from all analyses as they failed to exhibit detectable changes in skin conductance in response to the UCS (80dB - 100dB foghorn sound). Participants in the final sample (N = 14 per group) were matched on chronological age (Asperger mean = 29.7 yrs., SD = 10.2;

Comparison mean = 30.4 yrs., SD = 12.2) and WAIS-III^{UK} (The Psychological Corporation, 2002) full scale IQ (Asperger mean = 111, SD = 17.3; Comparison mean = 109, SD = 12.7). Individuals with Asperger's syndrome had all received their diagnosis according to conventional criteria (DSM-IV-TR, American Psychiatric Association, 2000; ICD-10, World Health Organisation, 1992) by experienced clinicians and none suffered any co-morbid anxiety disorders. The comparison group was recruited locally through newspaper advertisements. All individuals were free of medication and none of the participants exhibited discrepancies between verbal and non-verbal IQ of more than 15 points (i.e. 1.5 SDs), which could indicate neuropathology non-specific to ASD. The experimental procedures outlined below adhered to the ethical guidelines set out by the British Psychological Society and were approved by the University's Senate Ethical Committee. All participants were fully briefed before the experiment and all provided informed consent to participate in the study.

2.2. Materials & Design

The conditioning protocol was based on that employed by Bechara et al. (1995) and consisted of 12 habituation trials, 26 acquisition trials and 12 extinction trials. Four coloured slides (yellow, green, blue and red) presented for 2 seconds each on a Sony laptop 15'' monitor served as stimuli. One of these colours was designated CS+ and was to be followed by the UCS (1sec foghorn between 85 and 100 dB) during the acquisition phase of the protocol. The remaining colours were designated CS- and were never paired with the UCS. The choice of colour for CS+ was counterbalanced across participants. During habituation and acquisition, colours were presented at different frequencies in a fixed pseudorandom order (see Bechara et al., 1995 for details). The colour used as the CS+ stimulus occurred 5 times during the habituation phase and 12 times during the acquisition phase and appeared on the same trials for all participants. The remaining trials consisted of the CS- colours. The rate of presentation was one colour approximately every 10-30 seconds, dependent on the participants' skin conductance responses (a new stimulus was presented only when there was no sign of galvanic activity for at least 2 seconds). During the acquisition phase CS+ was reinforced according to a variable ratio schedule. Thus, six of the 12 occurrences of CS+ were immediately followed by the UCS ($CS+_{paired}$ trials), whereas the other 6 presentations of CS+ were not ($CS+_{unpaired}$ trials). During extinction, CS+ was presented repeatedly without any further presentations of the UCS. The illustration in Figure 1 summarizes this protocol.

INSERT FIGURE 1

Throughout the experiment, SCR was recorded via two surface electrodes attached to the medial phalanges of the first and third digits of the non-dominant hand (assessed by asking participants). Data were recorded using PowerLab hardware (ADInstruments, 2004), which sampled electrodermal activity at 1 kHz. Chart 5 software (ADInstruments, 2004) was used for the recording and assessment of the data. SCRs were computed according to standard criteria with the largest deflection during an 8 second window following the onset of a stimulus serving as a measure of autonomic response to that stimulus. All SCRs were square-root transformed prior to statistical analyses in order to normalise the distribution of the data.

2.3. Procedure

Participants were tested individually in a semi-soundproof air-conditioned room. They were warned that the experiment would involve hearing some startling noises, which were demonstrated at an initially low volume through speakers. All participants were then allowed to choose a volume level that they would find startling but in no way painful. Subsequent to the attachment of the electrodes, participants were asked to relax and find a comfortable seating position approximately 50 cm in front of the screen. They were asked to try and pay attention to the colours on the screen and to move as little as possible throughout the task in order to avoid movement artefacts. The experiment commenced following a few minutes during which SCRs were allowed to reach baseline activity. The experimenter was present throughout the whole of the procedure to control stimulus presentation and monitor SCRs. Seating arrangements were such that the participant was seated at approximately 1.5 m from the experimenter with no equipment apart from the attached electrodes and the presentation laptop in line of sight.

Following Bechara and colleagues (1995) participants' declarative memory of the experimental contingencies was probed around 5 minutes after the experimental procedure by asking them; 1) How many colours did you see? 2) What colours were they? 3) How many colours were followed by the loud noise? 4) What colour(s) was/were it/they? Correct responses to questions 1, 2

and 3 received a score of 0.5 whereas a correct response to question 4 received a score of 2.5, reflecting the fact that question 4 asks for the most important aspect of the experimental contingencies.

3. Results

Groups did not differ significantly in terms of the UCS intensities they chose (Asperger, M = 94dB, SD = 6; Comparisons, M = 97dB, SD = 3). Similarly, a 2 (group) x 6 (trial) mixed ANOVA of SCRs elicited during the 6 $CS+_{paired}$ trials of acquisition revealed no main effects or interactions (All Fs < 1). Thus, the UCS was similarly effective for both groups in eliciting startle responses and neither group seemed to habituate to the UCS during the acquisition phase. An analysis of participants' declarative knowledge revealed 100% accuracy for the comparison group but 5 of the Asperger participants made errors in response to at least 1 of the questions. Thus the Asperger group performed significantly worse in terms of noticing or remembering the experimental parameters ($U = 63$, $z = 2.41$, $p < .05$). As we will illustrate below, an assessment of individual data suggested that failing to remember the experimental contingencies was not directly related to autonomic fear acquisition, making it unlikely that the results described below are confounded by this group difference.

In order to assess the conditioning data we adopted a similar method to that of LaBar and colleagues (1995). Thus for our first analysis we computed difference scores by subtracting the average response elicited during CS- trials from SCRs elicited by each of the $CS+_{unpaired}$ trials. The resulting difference scores thus indicate to what extent SCRs during $CS+_{unpaired}$ trials exceeded the average response elicited by CS- presentations. Figure 2 illustrates these difference scores for the relevant five habituation and six acquisition trials as a function of group. For the analysis of these data the first acquisition difference score was omitted since in differential conditioning paradigms the association between CS+ and the UCS only becomes fully apparent after the second pairing between these stimuli. A 2 (group) x 2 (phase) x 5 (trial) mixed ANOVA revealed main effects for experimental phase (M habituation = -.07√μS, SD = .11; M acquisition = .27√μS, SD = .15; $F(1,26) = 50.11$, $p < .001$) and group (M Asperger = .03√μS, SD = .13; M Comparison = .17√μS, SD = .13; $F(1,26) = 8.00$, $p = .009$), which were further characterised by a phase x group interaction ($F(1,26) = 6.90$, $p = .014$). Post-hoc comparisons showed that this interaction was due to the fact that SCR difference scores were similar for both groups during habituation (M Asperger = -.08√μS, SD = .15; M Comparison = -.06√μS, SD = .15), whilst the Asperger group exhibited significantly attenuated difference scores relative to the

comparison group during the acquisition phase (M Asperger = .14√μS, SD = .21; M Comparison = .40√μS, SD = .21; F(1,26) = 11.30, p = .002). Importantly, however, separate analyses of the groups, revealed main effects of experimental phase for both the Asperger (F(1,13) = 13.27, p < .01) and the comparison group (F(1,13) = 37.59, p < .001). Thus, although participants with ASD exhibited attenuated fear acquisition in comparison to typical participants, the data confirm our prediction that individuals with Asperger's syndrome would show evidence of acquiring autonomic fear responses to a previously neutral stimulus.

INSERT FIGURE 2

The attenuation of difference scores in the Asperger group during acquisition could have several sources. First, it is possible that participants with Asperger's syndrome compared to typical participants exhibited either attenuated SCR responses to $CS+_{unpaired}$ stimuli or excessive responses to CS- stimuli during the acquisition phase of the protocol. Second, it is possible that only a subgroup of Asperger participants exhibited abnormalities to the effect of significantly reducing the groups' average in relation to the comparison group.

In order to assess these possibilities we carried out two further analyses. First we assessed SCRs separately for $CS+_{unpaired}$ and CS- stimuli as a function of group and experimental phase. Figure 3a and 3b illustrate these data and suggest that the attenuated differential fear acquisition in the Asperger group was largely the result of reduced SCRs to $CS+_{unpaired}$ stimuli during the acquisition phase of the experiment. A 2 (group) x 2 (phase) x 5 (trial) mixed ANOVA of these data (again the first $CS+_{unpaired}$ trial of acquisition was excluded) revealed a main effect of experimental phase (F(1,26) = 16.40, p < .001) confirming that $CS+_{unpaired}$ responses during acquisition (M = .66√μS, SD = .31) were higher than during habituation (M = .35√μS, SD = .17). Furthermore, the data were characterised by a significant interaction between experimental phase and trial (F(4,23) = 4.92, p < .01) and a marginal interaction between experimental phase and group (F(1,26) = 2.94, p = .098). Post-hoc analyses revealed that the interaction between experimental phase and trial was due to a decrease in responses over trials during habituation (F(4,23) = 3.86, p < .05) but not during the acquisition phase. The marginal interaction between phase and group was due to the fact that for the Asperger group the effect of experimental phase was only marginally significant (M habituation = .35√μS, SD = .24; M acquisition = .53√μS, SD

= .44; F(1,13) = 3.36, p = .090) whereas for the comparison group this effect was highly reliable (M habituation = .35√μS, SD = .24; M acquisition = .79√μS, SD = .44; F(1,13) = 14.00, p < .005). As Figure 3b suggests, responses to CS- stimuli were not characterised by any main effects or interactions[1].

INSERT FIGURE 3A and 3B

The analysis above suggests that the attenuated difference scores in the Asperger group are mostly attributable to an attenuation of SCRs to $CS+_{unpaired}$ stimuli during the acquisition phase. However, the magnitude of the standard errors illustrated in Figure 3a, together with the marginally significant effect of experimental phase of these data in the Asperger group, would also be consistent with the possibility that abnormalities in fear acquisition were present in only a subgroup of Asperger participants. In order to explore this possibility further, we carried out a second analysis and computed indices of fear acquisition and discrimination for each participant.

For the computation of these indices we considered the standard error of the mean habituation trials (hereafter SE_h) to reflect the error of measurement of SCRs of each individual, since these responses reflect galvanic activity during a relatively relaxed period and are therefore uncontaminated by the aversive stimulation that took place during acquisition[2]. For the index of acquisition, we subtracted the average SCRs to $CS+_{unpaired}$ trials during habituation from those to $CS+_{unpaired}$ trials during acquisition and divided this difference by SE_h. The resulting score thus represents the change in SCR to $CS+_{unpaired}$ trials between habituation and acquisition in units of the standard error of measurement, which has the advantage of removing inter-individual differences in baseline SCR variance from the data. For the index of discrimination, we subtracted the average SCRs to CS- trials during acquisition from the average SCRs to $CS+_{unpaired}$ trials during acquisition, again dividing the result by SE_h. This index thus provides the magnitude by which responses to $CS+_{unpaired}$ trials during acquisition exceeded responses to CS- trials during acquisition. The data for these indices, together with the values for SE_h are set out in Table 1. Based on the t-criterion one can consider an individual to

[1] Note: For the analysis of these data, responses during the 14 CS- trials during acquisition were averaged across blocks of two consecutive trials.

[2] Note: In fact there was no significant difference in the standard error of measurement between the habituation and acquisition trials, indicating that the presentation of aversive stimuli did not seem to increase the error variance in measurements of SCR activity.

have acquired fear if the acquisition index falls above 2. According to this criterion, 7 Asperger and 9 typical participants exhibited reliable fear acquisition to the CS+ stimulus, with 1 additional Asperger participant falling just short of the criterion. Closer inspection of these data furthermore suggest that with the exception of two typical participants who exhibited extremely high acquisition indices, the distribution of acquisition scores is relatively similar for the two groups. In fact, neither the group averages ($Z = 1.06$, $p = .291$), nor the proportions of participants reaching the criterion value of 2 ($X^2 = .58$, $df = 1$, $p = .352$) are statistically significant. Thus, on the basis of the acquisition indices, and in line with the findings by Bernier and colleagues (2005), we obtained no reliable evidence to suggest that participants with Asperger's syndrome differed from typical participants in terms of generally acquiring autonomic fear responses to a previously neutral stimulus.

INSERT TABLE 1

In contrast to this relatively typical level of fear acquisition, the data in table 1 indicate that participants with Asperger's syndrome compared to typical participants did not seem to acquire fear responses discriminately to CS+ and CS- stimuli during the acquisition phase. Compared to 11 of the typical participants who exhibited discrimination scores of at least 2, only 4 participants with Asperger's syndrome reached this criterion. This difference is statistically reliable both at the group level ($Z = 2.39$, $p = .017$) and in terms of the difference in the proportion of participants within each group who reached the criterion value of 2 ($X^2 = 7.04$, $df = 1$, $p = .011$). It is important to note that, since our indices of acquisition and discrimination are normalized against the standard error of the 12 habituation trials, it is possible that our analyses of these indices are confounded by group differences in baseline variability of SCRs (i.e. SE_h). As the data set out in Table 1 indicate, however, SE_h was similar for the two groups ($t = 1.35$; $df = 26$; ns)[3].

Several other aspects of these data merit further comment. First, it may seem paradoxical that two typical participants, who did not reach the criterion value of 2 for the acquisition index, reached

[3] Note: It is also worth noting that although the indices of acquisition and discrimination are highly correlated, even when the typical individual with indices greater than 30 is excluded (Asperger group: $r(12) = .723$, $p < .01$; Comparison group: $r(11) = .762$, $p < .01$), an analysis of covariance on the discrimination index with the acquisition index as the covariate still reveals a main effect of group ($F(1,24) = 5.02$; $p < .05$). This furthermore confirms a relatively specific impairment in discriminate fear acquisition in our Asperger group.

this criterion for the index of discrimination. Closer inspection of the data for these individuals revealed that they had not fully habituated during the 12 habituation trials. During the acquisition phase, however these individuals seemed to learn that the CS- colours were 'safe' as indicated by a decrease in SCRs during these trials over the course of acquisition. In contrast CS+ trials continued to elicit relatively high responses. Thus although SCRs for these individuals during CS+ trials did not increase during acquisition, the fact that their responses to CS- trials decreased indicates that they successfully learned the differential significance of CS- and CS+ stimuli. Although relatively view studies report intersubject variability of fear acquisition in paradigms such as the one used here, our observation that 78% of our comparison participants reliably acquired fear closely resembles the 80% reported by Phelps, Delgado, Nearing and LeDoux (2004). A related issue concerns our observation that 3 Asperger and 1 typical participant exhibited reliable acquisition scores in the wrong direction. On the basis of these data one may question the validity of the acquisition index as a measure of fear acquisition. However, these negative acquisition indices simply reflect that rather than acquiring fear to the CS+ stimulus, the individuals continued to habituate to this stimulus throughout the acquisition phase. In other words, these individuals simply failed to acquire fear rather than acquiring fear in the wrong direction, which would be indicated by a reliable negative discrimination index that was not observe for any individual. Finally it is worth pointing out that the individuals with Asperger's syndrome who did not receive maximum scores on the questions probing their declarative knowledge about the experimental contingencies (highlighted in bold font in Table 1) are not clearly identifiable in terms of their conditioning responses. Thus it seems unlikely that the attenuated level of differential autonomic conditioning in the Asperger group is due to some of these individuals failing to correctly recall the experimental contingencies.

4. Discussion

In the current experiment we examined differentially conditioned autonomic fear responses in a sample of participants with a diagnosis of Asperger's syndrome and matched typical comparison participants in order to gain further insights into emotional processing difficulties and the functional integrity of the amygdala in ASD. On the basis of the relevant literature we hypothesised that 1) participants with Asperger's syndrome would exhibit typical levels of autonomic responses to aversive stimulation 2) that they would exhibit evidence of acquiring autonomic fear responses to a previously

neutral stimulus and 3) that they would show an attenuated level of discriminate fear responses to conditioned and non-conditioned stimuli.

Our results were largely in line with our predictions. Groups were equivalent in terms of their baseline galvanic activity and their autonomic responses to an unconditioned aversive noise. An analysis of differential fear responses revealed that although individuals with ASD exhibited attenuated fear responses in comparison to typical participants, they did show a residual level of differentially acquired fear. In an attempt to identify the source of this atypical pattern of differential fear acquisition we carried out additional analyses, which indicated that although individuals with ASD were not impaired in acquiring fear per se, their learned fear responses to the conditioned stimulus did not differ reliably from autonomic responses to non-conditioned stimuli. It is important to note that this pattern of findings was not due to individuals with ASD acquiring fear to both the conditioned and non-conditioned stimuli but rather the result of significantly attenuated fear responses to the former.

At first glance, our observation of impaired differential fear acquisition in ASD may seem at odds with the intact acquisition of potentiated startle responses reported by Bernier et al., (2005). Particularly on the basis of our separate analyses of SCRs to CS+ and CS- stimuli, one may argue that in the current study ASD is characterised by general impairments in acquiring fear. Although the current data do not allow us to refute this possibility conclusively, there are several reasons why we argue that individuals with ASD are characterised by impairments in fear discrimination rather than fear acquisition. First, our group analyses revealed a residual level of fear acquisition in ASD, which together with the findings by Bernier et al. (2005) suggest that a gross impairment in the processes necessary for fear acquisition are not likely to be present in this disorder. Second, an assessment of individual data indicated that an equivalent number of participants in both groups reliably acquired fear to the conditioned stimulus. Most importantly, however, we feel that the attenuated level of fear acquisition to CS+ in our Asperger group needs to be interpreted within the context of the differential fear conditioning paradigm employed here. Such paradigms differ from simple conditioning paradigms such as the one employed by Bernier and colleagues (Bernier et al., 2005) in that the presentation of the conditioned stimulus is mixed with other neutral stimuli (i.e. CS-). In addition, unlike Bernier and colleagues (2005) who employed a 100% reinforcement schedule we utilized a 50% reinforcement schedule such that the CS+ stimulus was paired with the UCS on only half of its occurrences during

the acquisition phase. Both of these factors make the CS+ stimulus a less reliable cue for the UCS and although additional studies will be needed to clarify what aspects of the experimental contingencies contribute to the atypical pattern of fear acquisition in ASD, we argue that the additional complexity of differential conditioning paradigms underlies the impairment in fear acquisition in ASD.

As we have noted in our introduction, the additional complexity of differential fear conditioning paradigms requires cortical modulation of the sub-cortical amygdala system that mediates fear responses (Jarrell, et al., 1987; Morris et al., 1997). Our results thus lend support to the notion that atypical amygdala function may play a central role in the neuropathology characterising the disorder (e.g. Bachevallier, 1994; Bachevallier, 2000; Baron-Cohen et al., 1999; Baron-Cohen et al., 2000; Fotheringham, 1991; Howard, et al., 2000; Sweeten, et al., 2002). However, rather than a basic amygdala abnormality, our findings suggest that atypical amygdala function may arise from poor connectivity between this structure and functionally associated cortical areas. As noted in our introduction, this conclusion is in line with increasing evidence suggesting that ASD may be characterised by an underconnectivity of disparate brain regions (e.g. Belmonte et al., 2004; Brock et al., 2002; Rippon et al., in press). The only direct evidence for this suggestion to date stems from functional imaging studies involving tasks assessing sentence comprehension (Just et al., 2004), executive function (Just et al., in press), working memory (Koshino, Carpenter, Minshew, Cherkassky, Keller & Just, 2005) and mental state attribution (Castelli et al., 2002), all of which concluded that intra-cortical connectivity is atypical in ASD. Although, Ben Shalom (2000) has suggested that poor connectivity between the amygdala and cortical areas may constitute a source for the emotional processing atypicalities in ASD, to the best of our knowledge, our study constitutes the first behavioural evidence to directly support this view. In this context it was unfortunate that we were unable to assess the extinction phase of our protocol. Since fear extinction has also been shown to rely on interactions between the cortex (particularly the medial prefrontal cortex) and the amygdala (Morgan, Romanski & LeDoux, 1993; Morgan, Schulkin & LeDoux, 2003; Phelps, et al., 2004; Quirk, Russo, Barron & Lebron, 2000), we would predict atypical extinction learning in ASD. However, since the majority of ASD participants exhibited marked abnormalities in acquiring differential fear responses in the current paradigm, it would be impossible to interpret results from the extinction phase meaningfully. More specifically, any atypicality of fear extinction could either reflect atypical extinction processes or be a side-effect of the atypical pattern of fear acquisition. Equally, equivalent

fear extinction between groups would not necessarily indicate typical extinction processes in ASD since the possibility remains that atypicalities would arise if both groups acquired fear to similar extents. Future studies may be able to assess fear extinction more closely by employing simple conditioning paradigms, which as the study by Bernier and colleagues has demonstrated, lead to relatively typical patterns of fear acquisition in this population (Bernier et al., 2005).

Regardless of the neurological basis of the attenuated differential fear acquisition in ASD, our finding that such atypicalities exist at least behaviourally in this condition bears some important implications for our conceptualisation regarding the role of atypical emotional processes in the clinical manifestations of ASD. Since the acquisition of fear is amongst the most basic mechanisms by which an individual, and indeed any organism, learns about the emotional significance of sensory stimuli, our findings provide strong support for Hobson's (1989) suggestion that individuals with ASD are characterised by difficulties in understanding the hedonic value of their sensory-motor environment. Although future research will be needed in order to determine when such abnormalities emerge in ASD, it seems likely that this aspect of emotional development would play an important role in the aberrant development of affective behaviours in this condition. Thus, whilst difficulties in processing faces and theory of mind understanding may further contribute to the socio-emotional atypicalities manifest in ASD (e.g. Baron-Cohen et al., 2000; Schultz, 2005), it seems no longer plausible to suggest that atypicalities in these relatively complex socio-cognitive capacities are solely responsible for the clinically defining feature of this condition.

Our findings also bear some important practical implications for the design and implementation of behavioural intervention programmes. Several programmes that are currently in use, especially those based on the findings by Lovaas (1987), draw on operant conditioning principles to aid children in their learning. Similar to classical conditioning, operant conditioning mediates learning by means of association, although in this case the relevant associations are between an individuals own behaviour and an emotionally significant consequence (i.e. 'reward' or 'punishment') rather than between a neutral and an emotional stimulus. Another parallel between classical and operant conditioning, is that both types of learning are mediated primarily by the amygdala (see Aggleton, 2000 for detailed reviews). Given our findings, the question thus arises whether operant conditioning provides an effective way of mediating learning in ASD. Based on our findings we fear that the answer

to this question might be no. In fact, one of the most common problems therapists working on such programmes report, is that children with ASD often struggle to either generalize their learned responses to relevant problems outside of the immediate context or discriminate their responses adequately to different but related stimuli (e.g. learning the names of different animals or the letters of the alphabet). Although such reports are merely anecdotal, they underline the importance for further investigations in this area.

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Figure Legends.

Figure 1

Experimental procedure for the differential fear conditioning paradigm.

Figure 2

Skin conductance difference scores ($CS+_{unpaired}$ – average CS-) during habituation and acquisition for the Asperger and Comparison groups. Error bars show standard errors.

Figure 3a

Skin conductance responses to CS+ presentations during habituation and acquisition for the Asperger and Comparison groups. Error bars show standard errors.

Figure 3b

Skin conductance responses to CS- presentations during habituation and acquisition for the Asperger and Comparison groups. Error bars show standard errors.

Table 1

Indices of acquisition and discrimination for each participant in the Asperger and Comparison group. For clarity the data within each group have been arranged in descending magnitude of the acquisition index.

	Asperger Group			Comparison Group		
Participant #	SE_h	Acquisition index	Discrimination index	SE_h	Acquisition index	Discrimination index
1[c]	0.055	7.462[a]	5.150[b]	0.025	43.965[a]	31.686[b]
2	0.165	6.889[a]	1.779	0.126	11.468[a]	4.656[b]
3	0.062	5.761[a]	3.777[b]	0.082	7.288[a]	7.341[b]
4	0.070	4.745[a]	-0.619	0.073	5.559[a]	3.764[b]
5[c]	0.043	3.506[a]	2.550[b]	0.083	4.443[a]	4.893[b]
6	0.105	2.581[a]	1.558	0.083	4.097[a]	3.861[b]
7	0.112	2.416[a]	3.060[b]	0.125	3.071[a]	3.350[b]
8	0.044	1.970	0.991	0.174	3.029[a]	2.404[b]
9[c]	0.096	1.019	0.633	0.132	2.140[a]	2.012[b]
10	0.083	-0.644	0.288	0.089	1.080	-0.085
11	0.103	-1.891	1.217	0.119	1.022	3.170[b]
12[c]	0.035	-2.160	-1.756	0.100	0.237	2.608[b]
13	0.098	-2.923	0.011	0.059	-0.279	1.821
14[c]	0.042	-7.822	-1.218	0.103	-2.313	-0.114
Group Median	**0.076**	**2.193**	**1.104**	**0.095**	**3.050**	**3.260**

[a] Acquisition index scores that indicate reliable fear acquisition

[b] Discrimination index scores that indicate reliable differential fear responses

[c] Asperger participants who did not recall all aspects of the experimental contingencies.

Figure 1:

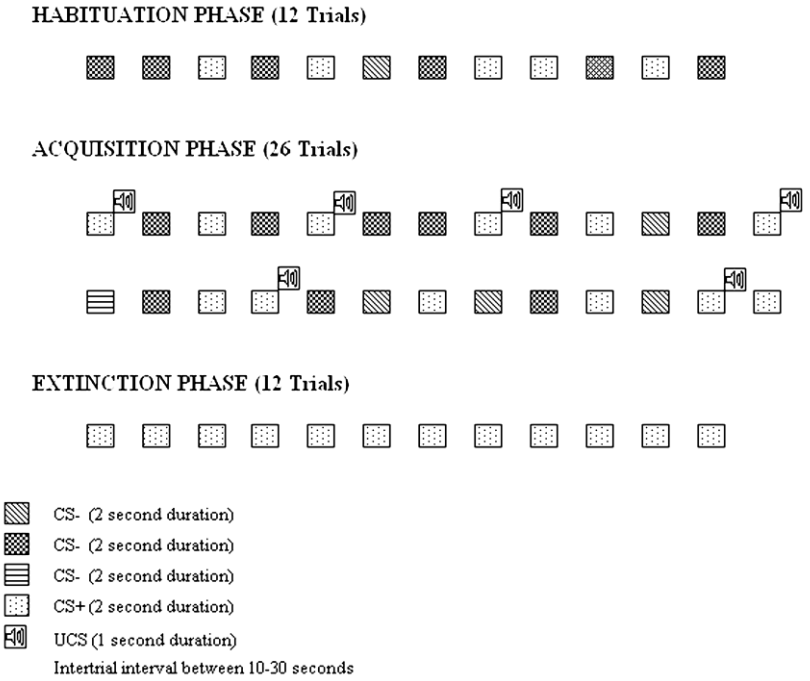

Figure 2:

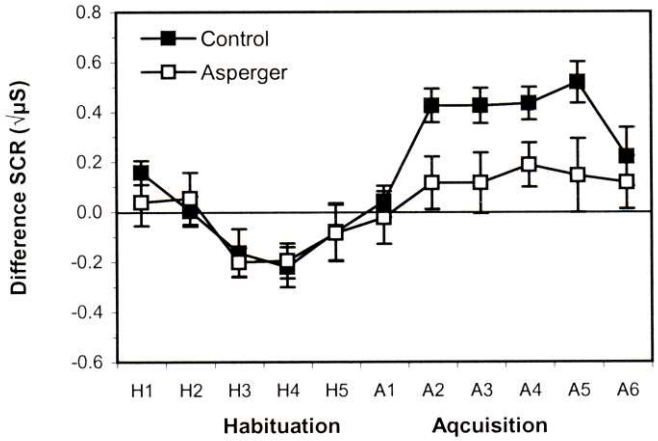

Figure 3A

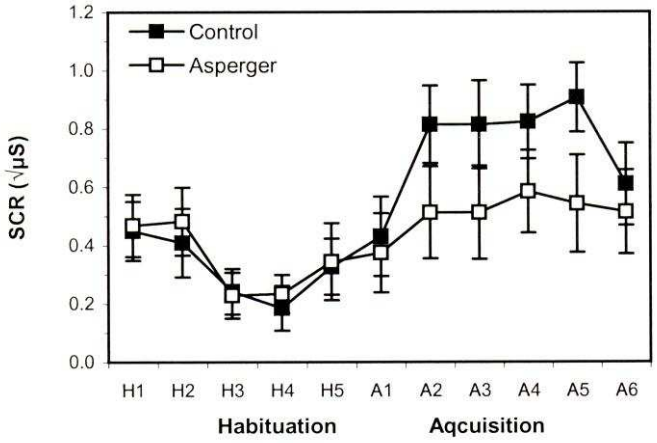

Figure 3B