

Individuals with Autism Spectrum Disorder Show Normal Responses to a Fear Potential Startle Paradigm

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The present study utilized a fear potentiated startle paradigm to examine amygdala function in individuals with autism spectrum disorder. Two competing hypotheses regarding amygdala dysfunction in autism have been proposed: (1) The amygdala is under-responsive, in which case it would be predicted that, in a fear potentiated startle experiment, individuals with autism would exhibit decreased fear conditioning and/or potentiation, and (2) The amygdala is over responsive, in which case an exaggerated potentiation of the startle response would be predicted. Fourteen adolescents and adults diagnosed with autism spectrum disorder and 14 age, gender, IQ, and anxiety level-matched typical adolescents and adults participated. Both participants with autism and typical participants potentiated the startle response following fear conditioning and no group differences in the latency or amplitude of the potentiated startle response were found. These results suggest that this aspect of amygdala function, namely fear conditioning and potentiation of the startle response, is intact in individuals with autism.

KEY WORDS: Autism spectrum disorders; amygdala; fear conditioning; potentiated startle.

INTRODUCTION

Autism is a neurobiological disorder characterized by impairments in the domains of social interaction, language and communication, and restricted or repetitive interests and behaviors. Profound impairments in social behavior are believed to be core to the syndrome. While many brain structures and pathways have been suggested to play a role in the disorder, the neurological basis of the disorder is not well understood. A better understanding of the neurobiology of autism would allow for a deeper

understanding of the cause of this disorder and more accurate diagnostic measures.

Researchers have proposed that amygdala dysfunction is a core feature of autism (Baron-Cohen *et al.*, 2000; Schultz *et al.*, 2000). This is based, in part, on autopsy, animal lesion studies, and functional imaging studies that have implicated the amygdala in autism and social behavior. In 1970, Kling and colleagues (Kling *et al.*, 1970) studied vervets with amygdala lesions in the wild. The lesioned vervets were unresponsive to their group, failed to display appropriate social signals, withdrew from social interaction and were frequently killed by other members of the group. Amygdala lesioned monkeys fail to initiate social interaction or respond to other monkey's gestures (Kling & Brothers, 1992), display flat vocalizations that lack affect (Newman & Bachevalier, 1997), and demonstrate reduced maternal behaviors, such as suckling, cuddling, and protecting their offspring (Bucher *et al.*, 1970). Such

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lesions also disrupt the dominance hierarchy (Rosvold *et al.*, 1954), and when lesions are made during infancy, such disruptions persist into adulthood (Thompson *et al.*, 1977). Lesions of the amygdala and related structures of the temporal lobe in rhesus monkeys result in Kluver and Bucy syndrome, which is characterized by decreased emotionality, a loss of fear, and the indiscriminate approach to both animate and inanimate objects (Kluver & Bucy, 1937). Bachevalier, after bilaterally lesioning the medial temporal lobe, including the amygdala, in infant monkeys found a subsequent lack of eye contact, social withdrawal, a failure to initiate social interactions, a lack of facial expression, and increased motor stereotypes (Bachevalier, 1994). However, Amaral and colleagues, in their recent work with maternally reared rhesus monkeys, have found that amygdala lesions do not impair the ability to recognize species typical social cues. Following bilateral lesioning of the amygdala at 2 weeks of age, these infant monkeys displayed a range of social behaviors and demonstrated no differences in eye gaze as compared to controls (Amaral *et al.*, 2003). Animal studies have provided some support for the amygdala's role in social functioning, but these recent findings question the extent of the structure's involvement.

The amygdala has also been implicated in social functioning in humans. Functional neuroimaging studies have found amygdala activation during processing of social information, including direction of eye gaze, facial expression, and race evaluation (Kawashima *et al.*, 1999; Morris *et al.*, 1996, 1998; Ohman, 2002; Phelps *et al.*, 2000; Whalen *et al.*, 1998; Wicker *et al.*, 1998). Studies examining patients with amygdala damage in the right hemisphere found impairments in emotion perception, specifically facial expressions of fear (Adolphs *et al.*, 1994; Anderson *et al.*, 2000; Calder *et al.*, 1996). Others have found variable levels of impairments in fear processing in amygdala lesioned patients (Adolphs *et al.*, 1999; Hamann *et al.*, 1996; Schmolck & Squire, 2001).

Research has also directly linked amygdala abnormalities to autism. An autopsy study of individuals with autism found increased cell density and decreased neuronal size in the amygdala (Bauman & Kemper, 1994), as well as other medial temporal lobe structures and the cerebellum. There is MRI evidence of enlarged amygdala in autism early in life and subsequent reduced amygdala volume later in life. Sparks *et al.* (2002) found that 3–4 year old children with autism showed larger than normal

whereas reduced amygdala volume was found in adult individuals with autism (Abell *et al.*, 1999). In a functional MRI study, Baron-Cohen and colleagues found reduced amygdala activation on tasks requiring identification of gender and mental state based on cues from the eyes compared to typical controls (Baron-Cohen *et al.*, 1999).

There are currently two competing hypotheses regarding the role of amygdala dysfunction in individuals with autism. The first is based on functional MRI research that suggests that the amygdala is hypo-responsive (Baron-Cohen *et al.*, 2000). This hypothesis posits that, in autism, the amygdala fails to assign emotional relevance to social stimuli. This results in a lack of interest in social relationships. The second view is that the lateral nucleus of the amygdala is in fact making these associations but is hyper-responsive. This hyper-responsivity then leads to a withdrawal from emotionally arousing stimuli. Such hyper-responsiveness has been found in individuals at risk for or diagnosed with anxiety disorders. For example, using fear potentiated startle paradigms, increased startle has been found in adults diagnosed with post-traumatic stress disorder (Grillon & Morgan, 1999; Grillon *et al.*, 1996; Morgan *et al.*, 1997) and children and adolescents whose parents have anxiety disorders (Grillon *et al.*, 1997, 1998).

Schultz and colleagues support the hyper-responsivity hypothesis noting the presence of heightened anxiety in social situations in some individuals with autism (Schultz *et al.*, 2000). Furthermore, relatives of individuals with autism are at increased risk for social anxiety compared to the general population (Murphy *et al.*, 2000; Piven, 2001).

In the current study, we utilized a fear-conditioning paradigm to study amygdala functioning in individuals with autism. Fear conditioning is a form of Pavlovian conditioning in which a subject is trained to associate a neutral stimulus with an aversive, unconditioned stimulus. Following the pairing the neutral stimulus when presented alone, acts as a conditioned stimulus and elicits a fear response. LeDoux's work on fear conditioning has demonstrated the amygdala's critical role in fear conditioning. In his series of studies in rats, he found that amygdala lesions result in a failure to make an association between a neutral stimulus that is paired with an unconditioned aversive stimulus as reflected in decreased emotional behaviors (increased heart rate, increased blood pressure, rat vocalizations, and freezing) to the neutral stimulus (LeDoux, 1996). In

further studies, LeDoux found that lesions of only the lateral nucleus of the amygdala blocked the association between the conditioned and unconditioned stimulus while lesions of the central nucleus only blocked the behavioral expression of fear rather than the association. Based on this line of research it is suggested that the temporal convergence of a stimulus and an emotional stimulus in the lateral nucleus of the amygdala allows for the association between the two and the assignment of emotional valence to that stimulus. Then, via the central nucleus, the emotional response is then expressed.

Fear conditioning has been linked to the amygdala in studies with humans as well. Fear conditioning deficits were found in individuals with damage to the amygdala (Bechara *et al.*, 1995; LaBar *et al.*, 1995). Functional MRI studies have found increased activation of the amygdala as a result of fear conditioning (Buchel *et al.*, 1998, 1999; LaBar *et al.*, 1998) or even the threat of aversive stimulus (Phelps *et al.*, 2001).

Fear potentiated startle is a fear conditioning paradigm in which the startle response, which is elicited by the sudden onset of an acoustic, visual, or tactile stimulus, is the dependent variable. The startle response is composed of a fast, series of muscle contractions which are most pronounced around the head, neck and shoulders. This response can be measured by the electromyographic activity around the eyes: the blink magnitude. The startle response, as measured by the eye blink latency and magnitude, is potentiated by the fear state induced through conditioning. The response has been potentiated by darkness in adults and children (Grillon *et al.*, 1997, 1999), threat of shock (Funayama *et al.*, 2001), aversive airpuff (Grillon & Ameli, 1998; Grillon *et al.*, 1999), lighting conditions (Basso, 2001), context conditioning (Ameli *et al.*, 2001), emotionally laden word presentation (Aitken *et al.*, 1999) and emotional pictures (Bradley *et al.*, 1990; Lang *et al.*, 1990). In addition, potentiated startle research has also demonstrated enhanced startle responses in

individuals with anxiety disorders. For example, Grillon and co-workers demonstrated an exaggerated startle response in patients diagnosed with PTSD (Grillon & Morgan, 1999) and children at genetic risk for anxiety disorders (Grillon *et al.*, 1997).

We utilized the fear potentiated startle paradigm to examine whether individuals with autism respond differently from matched control participants. If the hypo-activation hypothesis is correct, individuals with autism would be expected to show decreased potentiation compared to controls following conditioning, whereas if the hyper-activation hypothesis is correct, exaggerated potentiation compared to controls would be expected.

METHOD

Participants

Two groups of adolescents and adults ranging from 12 to 45 years of age participated in the study. The autism group was comprised of 12 males and 2 females with a diagnosis on the autism spectrum disorder (autism, pervasive developmental disorder—not otherwise specified (PDD-NOS), or Asperger syndrome) whose full scale IQ was between 87 and 129 (*M* = 106.1). The typical group was comprised of 12 males and 2 females whose full scale IQ was between 92 to 134 (*M* = 114.9). Descriptive information, including age, gender, and cognitive performance is summarized in Table I.

A diagnosis of autism, Asperger’s Syndrome, or PDD-NOS was based on the Autism Diagnostic Interview - Revised (ADI-R; Lord, Rutter, & LeCouteur, 1994), the Autism Diagnostic Observation Schedule - Generic (ADOS-G; Lord *et al.*, 2000), and clinical judgment of an experienced clinician based on DSM-IV-TR (American Psychiatric Association, 2000). Typical individuals were screened for a family history of autism or developmental disorders

Table I. Participant Characteristics

| Group | <i>n</i> | Age (years) | Full Scale IQ | State Anxiety (standard score) | Trait Anxiety (standard score) |
|----------|-------------------------|-------------|---------------|--------------------------------|--------------------------------|
| Autism | 14 (12 males 2 females) | 18.4 (5.5) | 106.1 (13.0) | 42.71 (9.80) | 52.07 (9.93) |
| Typical | 14 (12 males 2 females) | 19.7 (8.2) | 114.9 (12.5) | 44.14 (5.61) | 45.70 (6.59) |
| <i>F</i> | .236 | 3.322 | .224 | 3.897 | |
| <i>p</i> | | ns | ns | ns | ns |

Note: numbers represent means and standard deviations (in parentheses).

and were matched to the autism group based on age, gender, and cognitive abilities. Full scale IQs were measured using the Wechsler Scales of Intelligence (WISC-III or WAIS-III).

Individuals with autism were recruited from the University of Washington Autism Research Data Base and the University of Washington Autism Center. Typical controls were recruited from a listing of consenting participants from previous research studies at the University of Washington and through flyers placed throughout the campus and medical center. All participants and/or their legal guardians reviewed and signed consent forms approved by the IRB prior to participation.

Materials

Questionnaires

Assessment of state and trait anxiety was made using the State-Trait Anxiety Inventory (STAI; Spielberger, 1983). Participants completed the questionnaire following instructions and orientation to the experimental equipment and procedure while seated in the testing room immediately prior to beginning the experiment.

Stimulation Equipment

Psyscope software from an Apple Macintosh computer was used to program and run the experimental procedure. The aversive stimulus, an airpuff, was used in the first two phases of the experiment. The airpuff consisted of a burst of air directed at the throat through 4 mm internal diameter polyethylene tubing with a duration of 200 ms and a pressure of 60 psi (measured at the throat). Activation of the airpuff was controlled via a solenoid powered by an AC switch operated by the Psyscope software. Compressed air was stored in a cylinder behind a separating wall within the testing room and was connected to the solenoid via plastic tubing passing through a regulator. The acoustic startle stimulus used in all three phases of the experiment consisted of a 50 ms burst of white noise presented binaurally through headphones at 100 decibels.

Recording Equipment

The startle reflex was measured by eyeblink latency and magnitude using electromyographic (EMG) activity of the orbicularis oculi muscle.

Following recommendations for electrode placement by Fridlund and Cacioppo (1986), EMG activity was recorded using two Ag/AgCl surface electrodes placed under the left eye with a ground electrode placed on the forehead. The EMG signal was amplified and filtered using a preamplifier system (Electrical Geodesics Incorporated). Amplification was set at 1000 \times and filtering was conducted through a .1 Hz high pass filter and a 50 Hz elliptical low pass filter. The signal was digitized at 200 samples per second via an Analog to Digital converter (National Instruments PCI-1200) located in a second Apple Macintosh computer dedicated to data collection. The filtered EMG signal was recorded continuously on the computer's hard disk. The stimuli generating computer and the data collection computer were connected via serial port for precise synchronization and timing of stimulus onset and offset was recorded with the EMG activity for off-line segmentation of data.

Data Analysis Equipment

Eyeblink data were segmented and peak latency and amplitude were determined in the 20 to 100 ms window following stimuli presentation using a program written by the third author. The program used a peak-identifying algorithm. This algorithm scored, for each eyeblink, the amplitude from pre-stimulus point to peak in analog to digital (A/D) units as well as the latency to the peak. Latency to the peak was determined relative to the onset of the startle stimulus. Trials were rejected (less than 19% of total trials) if EMG activity during the first 20 s was excessive, if the blink did not return to baseline within the recording window, or if there was no blink response. The autism and typical groups did not differ in the number of rejected trials. The amplitude of the startle response was transformed into a standardized z score by subtracting the trial amplitude from the mean amplitude and dividing by the standard deviation. A T score was then computed by multiplying the z score by 10 and adding 50 following Grillon *et al.*, (1999).

Design and Procedure

Participants sat in a comfortable chair facing a blank computer screen and were instructed that they would periodically see different colors on the computer screen, hear a startling noise over the headphones, and periodically feel an airpuff from the plastic tubing draped over their neck.

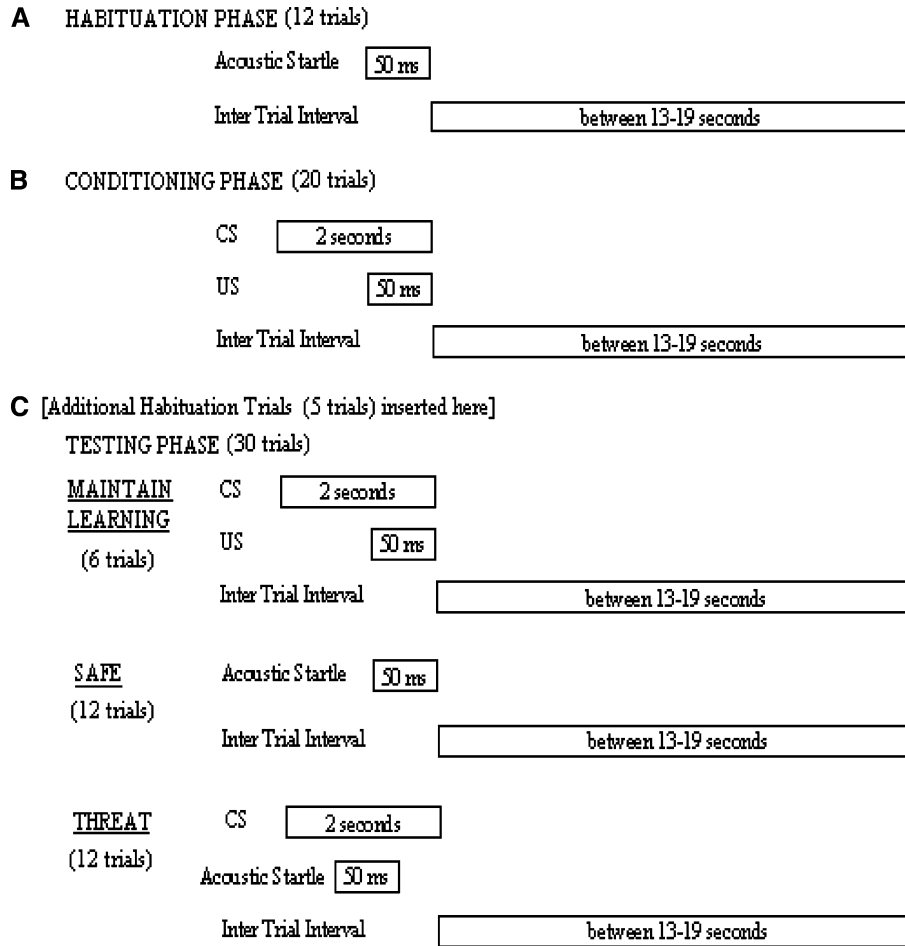


Fig. 1. Fear potentiated startle paradigm procedure.

In order to reduce initial reactivity, the experiment began with a habituation phase (see Fig. 1a) which consisted of one airpuff followed by a series of 12 acoustic startle probes presented between 13 and 19 s apart. During this period on the computer screen, a blank white screen was presented. The conditioning phase immediately followed this habituation period (see Fig. 1b). During the conditioning phase the participants were presented with the conditioned stimulus (CS), a red colored square presented on the computer screen, for 2000 ms. Presentation of the unconditioned stimulus (US), the aversive air puff overlapped for 50 ms and terminated simultaneously with the CS. Participants received 20 pairs of the CS (colored square presentation) and the US (aversive stimulus, air puff). The conditioning phase was followed by a second, short habituation phase that consisted of five presentations of the acoustic startle stimulus. The testing phase

then began (see Fig. 1c). The testing phase consisted of the presentation of 30 trials in randomized order so that participants would not be able to anticipate the next presentation. Six trials consisted of the CS and US pairing and were included to maintain the conditioning learned in the conditioning phase. Twelve trials consisted of the CS and acoustic startle stimulus. These trials served as the “threat condition.” The remaining 12 trials consisted of the acoustic startle stimulus alone. These trials served as the “safe condition.” During the CS and acoustic startle pairing, the startle stimulus was presented after 1000 ms of the CS onset. The acoustic startle was administered prior to the cessation of the CS to ensure that administration took place within the threat condition and consequently when the participant was most likely in a potentiated state. The time between each trial was between 13 and 19 s. The three phases of the procedure are presented in Fig. 1.

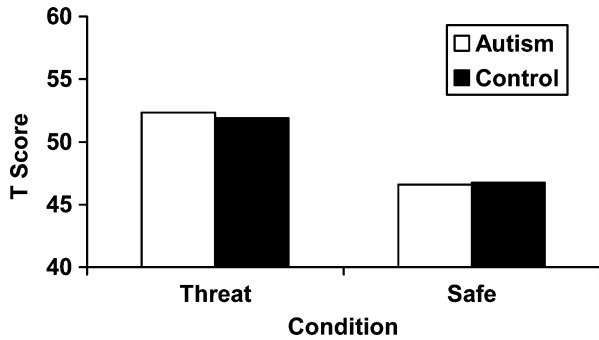


Fig. 2. Mean amplitude startle response (T score) for both autism ($n = 14$) and typical ($n = 14$) groups as a function of safe and threat conditions.

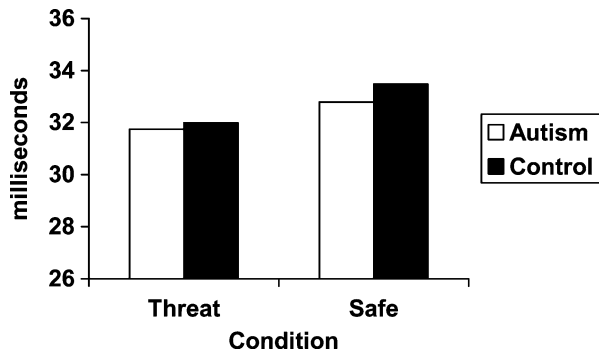


Fig. 3. Mean latency of startle response (ms) for both autism ($n = 14$) and typical ($n = 14$) groups as a function of safe and threat conditions.

RESULTS

The mean amplitude and mean latency of the startle response in the safe and threat conditions are presented in Figs. 2 and 3.

To examine the effects of group (autism and control) and condition (safe and threat), a mixed ANOVA was performed using amplitude of response as the dependent variable. A robust main effect for condition was found indicating potentiation to the conditioning, ($F_{1,26} = 44.808$, $p = .000$). No interaction or main effects involving group were found. Thus, both groups showed potentiation, but did not differ from each other in the magnitude of potentiation.

A similar analysis was performed utilizing latency of blink response as the dependent variable. Again, a main effect for condition was found for latency, ($F_{1,26} = 4.610$, $p = .04$), but there were no interaction or main effects involving group.

Growth curve analysis was used to examine habituation over the number of trials in each condition. No differences between groups in rate of habituation of amplitude or latency of response were found.

No differences were found between groups on levels of either state or trait anxiety as assessed by the STAI. However, for the typical group, controlling for age, partial correlations between the amplitude difference between the safe and threat conditions and state and trait anxiety were significant ($R^2 = -.5995$, $p = .030$; $R^2 = -.5886$, $p = .034$, respectively). That is, as state and trait anxiety increased, the amplitude difference between conditions decreased. This same pattern of correlation was not found for the autism group.

DISCUSSION

In the present study, it was found that both typical individuals and individuals with an autism spectrum disorder demonstrated similar potentiation to a threat condition following fear conditioning. These results suggest that the ability to develop associations between conditioned and unconditioned stimuli and utilize this association to modulate the startle response, which has been shown to be mediated by the amygdala, is intact and normal in individuals with autism. These findings are consistent with those of Salmond and colleagues (Salmond *et al.*, 2003) who utilized a startle modulation paradigm and also found no differences between autism and typical groups.

There are limitations to the conclusions that can be drawn, however. First, the sample consisted of individuals with autism whose cognitive abilities are in the average or above average range. Startle modulation is not a conscious or controlled process (Bradley *et al.*, 1999), therefore, it would follow that cognitive abilities would not be expected to affect startle modulation. Thus, a sample that performs poorer cognitively should not yield different results. Nevertheless, these findings need to be replicated in a sample of individuals with lower cognitive functioning as such individuals might also reflect a more severe form of the disorder. Amygdala functioning may vary with severity of the disorder.

Another caveat is that startle modulation examines functioning of only 2 of the 13 amygdaloid nuclei—the lateral and central nuclei. It might be that a different set of nuclei, which have roles yet to be determined, are more closely related to abnormalities in autism. Furthermore, although this study suggests

intact functioning of some aspects of the amygdala, it is important to note that the amygdala is a complex structure and this paradigm is only one avenue to explore this brain region.

Despite these limitations, there are conclusions that can be drawn. Most notable is that individuals with autism appear to have a different pattern of amygdala function than individuals with anxiety disorders. Individuals diagnosed with or at risk for anxiety disorders demonstrate enhanced startle responses (Grillon & Morgan, 1999; Grillon *et al.*, 1997). Grillon has suggested that enhanced startle is a physiological marker for anxiety (Grillon *et al.*, 1998). While anxiety is often reported in individuals with autism (Gillott *et al.*, 2001; Muris *et al.* 1998), the present findings suggest that the pathways involved in anxiety in typical individuals differ from that of individuals with autism. Were the pathways for anxiety in autism similar to anxiety in typical individuals, we would expect to find an exaggerated startle response.

It was surprising to note that the correlations between state and trait anxiety and the amplitude of the startle response for the individuals with autism differed from that of the control group. It could be that the autism group participants are not reporting their affective experience as accurately as the participants in the control group. Given the lack of previous research with the STAI and individuals with autism, it limits the strength of conclusions that can be drawn from this self-assessment test of anxiety. It would be important to utilize other forms of assessment of anxiety for future work in this area.

In summary, while several studies have suggested that amygdala dysfunction might exist in autism, the present study demonstrated normal function of a core aspect of the amygdala in a group of high functioning individuals with autism, thus highlighting the parameters to the amygdala's involvement in this disorder. However, future work could consider, in contrast to examining fear conditioning and the ability to attach negative valence to stimuli, the ability of individuals with autism to attach positive valence to environmental stimuli. More research is needed to clarify the specific role of the amygdala function in autism.

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