



Developmental changes in startle reactivity in school-age children at risk for and with actual anxiety disorder

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ABSTRACT

The present study examined the development of elevated startle reactivity in anticipation of mild anxiogenic procedures in school-age children with current anxiety disorders and in those at-risk for their development due to parental anxiety. Startle blink reflexes and skin conductance responses were assessed in 7 to 12 year old anxious children ($N=21$), non-anxious children at-risk for anxiety by virtue of parental anxiety disorder status ($N=16$) and non-anxious control children of non-anxious parents ($N=13$). Responses were elicited by 28 auditory startle stimuli presented prior to undertaking mild anxiogenic laboratory procedures. Results showed that group differences in startle reactivity differed as a function of children's age. Relative to control children for whom age had no effect, startle reflex magnitude in anticipation of anxiogenic procedures increased across the 7 to 12 years age range in children at-risk for anxiety disorders, whereas elevations in startle reactivity were already manifest from a younger age in children with anxiety disorders. These findings may suggest an underlying vulnerability that becomes manifest with development in offspring of anxious parents as the risk for anxiety disorders increases.

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Childhood anxiety disorders are among the most common and debilitating psychiatric disorders affecting children and adolescents (Cartwright-Hatton et al., 2006) and pose a significant risk for later anxiety disorders, depression, and conduct-related problems (e.g., Bittner et al., 2007; Merikangas et al., 1999; Pine et al., 1998). These disorders are associated with significant psychosocial impairment (Kessler et al., 1995; Velting and Albano, 2001), and a range of socio-economic costs if left to persist into adulthood (Waghorn et al., 2004). The investigation of children at-risk for anxiety disorders is one avenue for enhancing the understanding of premorbid risk factors that may play a role in the development of these disorders in children.

Parental anxiety is one of the strongest predictors of childhood anxiety, with the risk to offspring of anxious parents averaging 3.5 times (range 1.3 to 13.3) greater than the risk for healthy controls (e.g., Merikangas et al., 1999; Turner et al., 1987; Tillfors et al., 2001). However, risk factors themselves, such as parental anxiety, do not elucidate the mechanisms or pathways by which risk is conferred (e.g., Ormel et al., 2004). The tendency to react with elevated fear responses to

stimuli and situations that are relatively innocuous to others is an emotional hallmark of anxiety (Gray, 1982; Kagan et al., 1988; Grillon et al., 1997; Mogg and Bradley, 1998). The present study therefore examined whether elevated reactivity to putatively mild anxiogenic contexts, as indexed by the magnitudes of startle blink reflexes, is an underlying psychophysiological vulnerability by which risk associated with parental anxiety disorders manifests in offspring.

The human startle blink reflex is an ubiquitous response to intense stimulation with sudden onset and indexes defensive responding to aversive stimuli and associated contexts (see Davis, 1998, and Grillon and Baas, 2003, for reviews). Rodent studies have shown that modulation of the startle reflex by *aversive contexts* (such as long duration bright lights) is mediated by the bed nucleus of the stria terminalis, whereas fear-induced modulation of the startle reflex by *explicit threat cues* (such as a cue previously paired with an electric shock) is mediated by the central nucleus of the amygdala (Davis, 1998; Walker et al., 2003).

Numerous studies have shown that the magnitude of the startle reflex is increased in anxious adults compared with controls in contexts associated with threat but not in response to explicit threat cues. For example, Grillon and colleagues have shown that adults with panic disorder and posttraumatic stress disorder display sustained

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elevations in startle reflexes at the commencement of an experimental session that later involves the delivery of unpleasant electric shocks signalled by a cue. However, they do not differ from controls in startle reflex magnitudes elicited during explicit cues of threat (e.g., Grillon et al., 1994; Grillon et al., 1998a,b; Grillon and Ameli, 1998; Grillon and Morgan, 1999), or when explicitly informed that no aversive stimuli would be presented during the entire experimental procedure (e.g., Grillon et al., 1998a,b). Larger startle reflexes in anxious individuals are thought to represent increased anxiety about the laboratory context associated with later threat of an aversive stimulus (Grillon et al., 1998a,b). Grillon, Baas, Lissek, Smith, and Milstein (2004) concluded that “sustained contextual anxiety, but not phasic explicit cue fear, differentiates anxiety-disordered from non-anxiety-disordered individuals” (p. 916).

A small literature based on offspring at-risk for anxiety disorders by virtue of parental anxiety has shown that compared with low-risk offspring, at-risk youths (age range 7 to 18 years) display larger startle reflexes prior to as well as during darkness-induced fear-potential protocols and during threat of an air blast to the larynx (Grillon et al., 1997, 1998a,b; Merikangas et al., 1999). Similarly, offspring of anxious parents (age range 7 to 12 years) displayed significantly larger electrodermal activity prior to and during the inter-trial intervals while viewing and hearing fear-relevant stimuli relative to controls (Turner et al., 2005). Taken together, these studies suggest that anxiogenic contexts enhance psychophysiological indices of emotional reactivity (i.e., startle reflexes and electrodermal activity) in the offspring of parents with anxiety disorders.

To date, very little is known about whether contextually-enhanced startle reactivity is also characteristic of currently anxious children. In a study of high-risk offspring of anxious and alcoholic parents, Grillon et al. (1997) reported a trend for larger startle reactivity in offspring with any psychiatric disorder compared to offspring without any psychiatric disorders. In a study of clinically-anxious and non-anxious 4 to 8 year olds, Waters, Neumann, Henry, Craske, and Ornitz (2008) showed that initial startle reactivity did not differ between the two groups; however, anxious children showed sustained elevations of startle magnitude throughout a later affective modulation phase that involved the presentation of angry and neutral emotional faces. Thus, the present study aimed to extend these prior findings by comparing startle reactivity in anticipation of mildly aversive contexts in currently anxious children and high- and low-risk offspring of anxious and non-anxious parents respectively.

Based on interpretations of elevated startle reactivity during baseline phases prior to stressful laboratory procedures as reflecting on a context effect (e.g., Grillon et al., 2004), contextual enhancement in the present study was conceptualised as the potential anxiogenic effects induced by anticipation of mildly aversive laboratory procedures. These included loud auditory stimuli and emotionally threatening faces and ambiguous stories (see Waters, Craske, Bergman, and Treanor, 2008; Waters, Neumann et al., 2008) that children would encounter during their laboratory visit as well as by the experimental context itself (i.e., laboratory rooms, unfamiliar experimenters, electrode connections etc.).

If elevated startle reactivity in even mild anxiogenic contexts is an underlying vulnerability factor for childhood anxiety disorders that is associated with risk due to parental anxiety disorders, then startle reflex magnitude would be expected to be larger in at-risk and currently anxious children compared with controls. Group differences in rates of habituation were not expected given that previous studies have repeatedly shown comparable rates of startle habituation between high-risk offspring (e.g., Grillon et al., 1997, 1998a,b, 2005) and anxious children (e.g., Waters, Neumann et al., 2008) relative to controls. Skin conductance responses were recorded as a complementary measure of defensive responding to the startle eliciting stimulus. Finally, given some preliminary evidence of differences in startle reactivity due to anxiogenic contexts in young (i.e., 4–8 year old) anxious children

relative to controls (e.g., Waters, Neumann et al., 2008), we also conducted exploratory analyses to examine whether children's age (i.e., 7–9 vs 10–12) differentially affected startle reactivity.

1. Method

1.1. Participants

Participants were 50 children (28 boys; 22 girls) between 7 years, 0 months and 12 years, 9 months ($M=9.42$ years; $SD=1.62$). There were 21 anxious children, 16 at-risk children and 13 control children. At-risk children were recruited from parents attending the UCLA Anxiety Disorders Behavioral Research Program, and from advertisements within the local community and elementary schools in the Los Angeles area (with school district approvals). Anxious and non-anxious control children were recruited through the local community and elementary schools. All children were the biological offspring of their parents.

All children were assessed using the Anxiety Disorders Interview Schedule for DSM-IV – Child version (ADIS-C-IV; Silverman and Albano, 1996). Parents completed the lifetime version of the ADIS (ADIS-IV-L; Brown et al., 1994) regarding their own psychiatric status. In both schedules, interviewers assign a 0 to 8 point clinical severity rating (CSR) for each diagnosis, indicating level of distress/interference, with ratings of 4 or more representing clinical severity. Children and parents were deemed to have an anxiety disorder if they met DSM-IV criteria for an anxiety disorder with a CSR of 4 or greater.

1.1.1. Anxious group (ANX)

Children met criteria for a principal (i.e., highest CSR) anxiety disorder diagnosis of separation anxiety disorder, panic disorder, generalized anxiety disorder (GAD), or social phobia with a CSR of 4 or greater, or specific phobia with a CSR of 4 or greater if accompanied by another anxiety disorder diagnosis with a CSR of 3 or greater. Parental anxiety status was not taken into account. To reduce sample heterogeneity, children were excluded if their *principal* anxiety diagnosis was either obsessive compulsive disorder or posttraumatic stress disorder. Of the 21 ANX children (11 boys; 10 girls), 10 had a principal anxiety disorder diagnosis of GAD (mean CSR=4.5); 4 had social phobia (mean CSR=4.75), 4 had specific phobia (mean CSR=4.5), and 3 had separation anxiety disorder (mean CSR=5.3).

1.1.2. At-risk group (AR)

Either or both biological parents met criteria for a current or past anxiety disorder (beyond the age of 10) with a CSR of 4 or greater, whereas the child neither met criteria for any anxiety disorder nor exhibited subclinical anxiety symptoms with a CSR greater than 2, current or past. We elected either biological parent given the evidence that paternal anxiety confers the same risk as maternal anxiety (e.g., Connell and Goodman, 2002). We elected to exclude families in whom parental anxiety did not extend beyond the age of 10 as a way of setting a minimal level of risk and ensuring that the parental anxiety disorder was not a transient anxiety state during childhood. On the other hand, parental anxiety disorders were not required to persist throughout the life of the participating child, because patterns of familial aggregation, being at least partly explained by additive genetic factors (Kendler et al., 1992), are not solely reliant on parental ‘behavioral expression’. The 16 AR children (10 boys; 6 girls) did not meet criteria for any psychiatric disorder. Of these children, eight had a mother with a current anxiety disorder (4 with GAD (mean CSR=4.5), 3 with specific phobias (mean CSR=4.3), and 1 with social phobia (CSR=5) and one had a father with a current specific phobia (CSR=5). Four had mothers with a past anxiety disorder: 2 with past GAD (mean CSR=4.5), 1 with past social phobia (CSR=4) and 1 with past specific phobia (CSR=4). One had a father with past panic disorder (CSR=4). Both the mother and father of another child met criteria for multiple current and past

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