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The role of novelty in the development and maintenance of anxiety

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Elinor Loveday Butterfield (BScHons)

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ABSTRACT

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

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THE ROLE OF NOVELTY IN THE DEVELOPMENT AND MAINTENANCE OF ANXIETY

BY

ELINOR LOVEDAY BUTTERFIELD

A particularly influential theory of anxiety suggests that the anxious state is associated with hypersensitivity to novelty and/or ambiguity (Gray 1982), but this feature has attracted little attention. The increase in availability of neuroscience techniques offers an opportunity to directly explore brain function associated with novelty processing. In this study, auditory event-related potentials associated with unexpected novel noises were explored in normally developing children with low and high self-reported trait anxiety.

A total of 23 children participated in an event related potential study of novelty processing. The children were divided into low (n = 12) and high (n = 11) trait anxious groups according to a median split of STAIC (State-Trait Anxiety Inventory for Children) scores. A novelty auditory oddball paradigm was employed. This paradigm presents frequent low tones, and equally infrequent high tones and novel noises (e.g. dog bark). The amplitude and latency of two main components, the 'N1' and the 'P3' were compared between groups.

Significant effects were found between groups, confined to the N1 component. The N1 elicited by novel stimuli, was of longer latency ($p = .014$) and greater amplitude ($p = .004$) in the high compared to low anxious group. In support, significant linear correlations revealed that novelty-N1 amplitude increased with an increase in trait anxiety.

Brain response to novelty is modulated by increased trait anxiety in normally developing children. The subtle changes in brain activity extend previous event-related potential data obtained from high trait anxious children (Daruna, Rau, and Strecker, 1991) and children who are behaviourally inhibited (Bar-Haim, Marshall, Fox, Schorr, and Gordon-Salant, 2003). However, the present findings are unique in demonstrating a significant effect of stimulus novelty in the absence of stimulus-probability effects. This provides empirical support for the hypothesis of Gray (1982, 2000) that conflict associated with novelty and/or ambiguity may underpin the development and maintenance of anxiety disorders in childhood.

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Literature Review Paper

Brain and Behaviour in Children with Anxiety

Clinical Psychology Review was used as a guide in determining the preparation of this paper.

Abstract

Childhood anxiety is one of the most prevalent forms of psychopathology estimated to affect approximately 20% of children and adolescents at some point in their lives. Although previous research indicates that many anxiety disorders are transient and resolve within three to four years, there is also evidence to suggest that some remain stable across childhood and adolescence and can follow a chronic pathway into adulthood. They therefore present a significant challenge to clinical psychologists. In order to offer effective intervention clinical psychologists must have a solid theoretical basis. Gray (1982; Gray and McNaughton, 2000) hypothesised that anxiety is associated with conflict resulting from overactivation of the "behavioural inhibition system" (BIS). The BIS system is activated in a number of situations, including those that are ambiguous and/or novel. Activation of the BIS leads to increased vigilance and attention, and potentially to greater behavioural inhibition. Moreover, behavioural inhibition in childhood has been associated with diagnosis of anxiety disorder in later life. In this review, an overview of the importance of novelty processing in childhood and its related neuroanatomy is provided, followed by definitions and descriptions of our current understanding of anxiety, and those theoretical models that have proved particularly influential. Brain-behavioural processes underling anxiety may be tested using neuroscience techniques. In particular the event-related potential (ERP) technique is introduced and components associated with novelty processing described. Conclusions are drawn that bring together a description of how brain-behavioural processes associated with novelty processing may underpin the formation and development of anxiety, and how techniques such as ERP may offer a unique window into this relationship.

Overview

One of the most studied areas of psychopathology is that of anxiety and anxiety related disorders. A particularly influential theory of anxiety suggests that the anxious state is associated with hypersensitivity to novelty and/or ambiguity (Gray 1982), but this feature has attracted little attention.

The efficient processing of novel events is critical for biological adaptation (survival), e.g. a new sound might be a warning of imminent danger (Barlow, 1988; Friedman, Cycowicz and Gaeta, 2001), but, more generally, novelty-processing has also been associated with intellectual, cognitive and psychosocial development (Berg and Sternberg, 1985). Thus, there may be wider implications of abnormal novelty-processing, with regard to learning and emotional development.

This review will focus primarily on 'trait anxiety' and its impact upon the appraisal of novel and unexpected events from a cognitive and a biological point of view. Changes in the brain associated with strange (unexpected) situations have been described in infants and children using electroencephalography – EEG – techniques (e.g. Fox, Henderson, Rubin, Calkins, and Schmidt, 2001). It is proposed that event-related potentials – ERP - (which are derived from the EEG trace and more directly time-locked to the occurrence of a novel event) may provide complementary information about novelty-processing in anxious children. Indeed, ERP studies in non-anxious children have suggested that distinct patterns of activity associated with auditory novel stimuli may be detected from early in life (e.g. Määttä, Pääkkönen, Saavalainen, and Partanen, 2005a; Määttä et al., 2005b). Only two ERP studies have been published in anxious (Daruna, Rau and Strecker, 1991)

and behaviourally inhibited (Bar-Haim et al, 2003) children, and neither examined the effect of stimulus novelty in the absence of stimulus-probability effects.

This review will first give a brief overview of the importance of novelty processing in childhood and its related neuroanatomy. This will be followed by definitions and descriptions of our current understanding of anxiety; those theoretical models of anxiety that have proved particularly influential are described and critically discussed in relation to novelty processing (Beck, 1976; Clark, 1986). Increasingly, hypotheses derived from these models about brain-behavioural processes underlying anxiety are being tested using neuroscience techniques. While some neuroscience techniques may be inappropriate due to the anxiety elicited over and above that already experienced by the individual (e.g. MRI scanning), others (e.g. ERP) are less invasive, and particularly useful for examining brain-behavioural processes in the very young and the very old. The ERP technique is introduced and components associated with novelty processing described.

Thus, the aim of this review is to bring together a seemingly disparate literature, to describe how brain-behavioural processes associated with novelty processing may underpin the formation and development of anxiety, and how techniques such as ERP may offer a unique window into this relationship. It is intended to consider whether such information may provide empirical support for those models suggesting that abnormal novelty processing is associated with the anxious state.

1. Novelty Processing

The processing of novel events is essential to human behaviour and plays a critical role in adaptation and learning (Daffner et al., 1998; Mesulam, 1998; Sokolov, 1963). Research has shown that humans vary in the degree to which they actively attend to and explore novel stimuli in the environment (Eaves and Glen, 1996; Lewis and Brooks-Gunn, 1981; McCall, 1994), and links have been identified between low levels of attention to novelty and lower cognitive abilities in children and adolescents (Berg and Sternberg, 1985; Rose, Slater and Perry, 1986). It has also been hypothesised that the influence of attention to novelty may not only be limited to cognitive development but may also influence affective functioning as well (Eaves, Darch, and Williams 2004). In other words, the development of psychopathology, such as anxiety disorders, may emerge in those infants who are born with a low need for stimulation and a high level of sustained attention for novel stimuli. Studies examining the neural underpinnings of novelty appraisal implicate the frontal lobes in the processing of novel environmental events (Daffner et al., 1998, 2000, 2003). Behavioural and physiological features of inhibited and uninhibited temperaments are also hypothesised to be due to variation in temporal lobe (amygdala) response to novelty (Kagan, Reznick and Snidman, 1987, 1988a).

1.1. Novelty processing in normal child development

Novelty-processing in normal child development is at the same time associated with learning and exploration, and the development of fear of the unfamiliar. Both are adaptive features of child development. With regard to the former, the processing of novel stimuli is an important part of intellectual development; indeed this was a critical component of Piaget's theory of child intelligence (Piaget, 1954). In

infancy, children learn to explore the environment and process novelty from a secure base (e.g. mother/father), to which they return periodically for reassurance. This is considered to be one of the hallmarks of an 'attachment relationship' (Bowlby, 1969), and fear of unfamiliarity ('fear of strangers') and novelty, typically seen in infants of 7-9 months of age, is a normal and expected part of child development. The development of a healthy awareness and respect for the unfamiliar is also a survival mechanism in protecting the individual from harm (Barlow, 1988; Friedman et al., 2001). Notwithstanding the adaptive importance of developing a fear of the unexpected, other work on temperament has focused on early appearing signs of extremes of negative affect and its subsequent link to inhibition and shyness (Prior, 1992), and avoidance of novelty (Kagan et al., 1988a, 1988b). Importantly, studies have also suggested an association between behavioural inhibition and the onset of anxiety disorders in children (Biederman et al., 1993; Rosenbaum, Biederman, Hirshfeld, Bolduc, and Chaloff, 1991a; Rosenbaum et al., 1991b; Schwartz, Snidman, and Kagan, 1999; Van Ameringen, Mancini, and Oakman, 1998).

Thus, novelty-processing is associated with intellectual and social development, but in the context of extremes of personality, may be implicated in the formation and maintenance of abnormal levels of anxiety. Although perturbations in novelty-processing are not an overt feature of the anxiety literature, it is implicit in a number of influential theories and models. In order to demonstrate this it is necessary to examine the anxiety literature in greater detail.

2. Overview of the development and maintenance of the anxious state

Anxiety disorders are thought to result from abnormal processing of threat related stimuli (Beck and Clark, 1997; Eysenck, 1991), as well as functional deficits in the way the brain processes fear learning and memory (Barlow, 2000; Rosen and Schulkin, 1998). The consequences of anxiety can manifest in a number of different ways, but commonly involve excessive worry, intense physiologic signs of arousal such as sweating and palpitations, increased vigilance, behavioural avoidance and significant impairment in everyday functioning (Barlow, 2000; Kandel, 1983).

Cognitive models of emotional disorders such as anxiety postulate that it is not the events *per* se but rather an individual's expectations and interpretation of events which are responsible for the production of negative emotions, (Clark, 1986). In everyday life there are a number of situations that may be considered dangerous and therefore an individual's perceptions could be viewed as realistic appraisals of threat. However, it is argued that anxious individuals overestimate the danger in a given situation, automatically activating what Beck (1976) referred to as the 'anxiety programme'. This is a set of responses inherited from an evolutionary past, i.e. responses that may have originally protected against harm in a primitive environment. For example, changes in autonomic arousal prepare us for flight or fight, inhibition of ongoing behaviour enables attention to be focused on the perceived threat and selective scanning of the environment alerts us to sources of danger. Although such 'anxiety' continues to serve as a useful function in many modern day situations (e.g. being followed by a stranger in the dark), it may be

maladaptive when the threat arises from a misperception or over-attribution of the level of danger.

A distinction is often made between state anxiety, trait anxiety and anxiety disorders. Anxiety as a state is similar to phobic anxiety in that it can be associated with a well-defined and identifiable threatening stimulus such as a spider, and is temporary (Cattell and Scheier, 1958). Trait anxiety is a more enduring disposition. It is typically generalised and not restricted to a specific cue: 'free-floating' (Grillon, 2002). In this situation, there is a chronic tendency for the individual to show an anxiety response to environmental events (Perez-Edgar and Fox, 2005). Negative thoughts associated with trait anxiety are varied but often revolve around being unable to cope, the anticipation of a negative evaluation from others, performance fears and somatic concerns. Importantly, high levels of trait anxiety may lead to a diagnosis of generalised anxiety disorder (GAD), simple phobia, social phobia, panic disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). Together these disorders are believed to affect over 20% of the adult population at some point in their lives, with variable impact on an individual's physical, social and emotional state (Greenberg et al., 1999).

As previously stated, a common assumption is that anxiety results from the (over)activation of those defence mechanisms that are essential for survival (LeDoux, 1995; Rodgers, 1997). According to this view, symptoms of pathological anxiety are frequently the response of an inappropriate activation or hypersensitivity of normally adaptive defence systems. Most animals from lower invertebrates to man have a tendency to be alerted and frightened by unexpected events such as loud

noises, bright lights or unfamiliar/novel objects (Cloninger, 1986). However, in most cases animals and humans may habituate to such events once they become familiar (Cloninger, 1986). Habituation may thus be interpreted as the ability to learn to disregard stimuli that are evaluated as without significance (Houtveen, Reitveld, Schoutrop, Spiering, and Brosschot, 2001). An advantage of this is that the individual can screen out 'noise' and focus attention on other activities.

Many individuals prone to anxiety are observed to have a reduced tendency to habituate to such stimuli, and this is associated with chronically increased physiological responses (e.g. galvanic skin responses), and the maintenance of a high level of perceptual sensitivity and vigilance (Cloninger 1986; Martin-Soelch, Stocklin, Dammann, Opwis, and Seifritz, 2005). This hypersensitivity may also be viewed as an elementary form of non-associative learning (Dilger, 1980). In other words, following exposure to unpredictable, aversive or novel stimuli, the individual learns to strengthen its defensive response and thereafter respond in a similarly defensive manner to stimuli that were previously neutral (Castellucci and Kandel, 1976). This leads to sensitisation, which is frequently viewed as analogous to chronic 'free-floating' anxiety in which feelings of nervousness and tensions cannot be attributed to obvious external threats (Kandel, 1983).

Fear conditioning is a form of classical or associative learning that in its most basic form involves the connection of a neutral stimulus and an aversive stimulus. Although this connection is learned, the response to the threat is not and can be viewed as an automatically activated response system ('cue-specific' fear see LeDoux 1995) when confronting threatening stimuli (LeDoux, 2000). This theory

which is mainly based on animal models is nevertheless useful to a discussion of novelty-processing in human anxiety, as fear conditioning produces similar response patterns in both animals and humans, i.e. avoidance behaviour, changes in level of vigilance, and autonomic regulation. In support, adult and child studies demonstrate that individuals with anxiety disorders can exhibit enhanced subjective and physiological responses to a standard set of mildly threatening stimuli or situations (Barlow 2002; Birbaumer et al., 1998; Lang, Bradley, Cuthbert, 1998; Pine et al., 2000), suggesting that they may differ in their level of learned-sensitivity to such stimuli from non-anxious individuals.

The orienting response may be described as a reflexive and involuntary redirection of attention that interrupts the thought process to allow the individual to decide whether or not a novel or unexpected event requires further processing. This is a part of everyday life for all species, e.g. the perception of environmental change. The ability to rapidly orient to previously unattended stimuli is an important element of attention, and develops early in life (Grillon, 2002). For example, individual differences in the orienting response have been related to autonomic conditioning in 3 month-old infants (Ingram and Fitzgerald, 1974), and to discrimination learning in childhood (Cousins, 1976). The possibility exists that anxious individuals have a heightened orienting response, leading to deficits in cognitive (e.g. attention is too readily diverted from the task-at-hand), emotional (e.g. abnormalities of the orienting response may lead to fear of new situations), and behavioural (e.g. avoidance of new situations) development from a very young age and contribute to the development of anxiety disorders in children. In support, the

early studies by Kagan and colleagues (1987, 1988) described behaviourally-inhibited children as hyper-vigilant.

The literature on the effects of ambiguous (potentially uncontrollable and aversive) events provides important insights into features of anxiety disorders associated with contextual fear and the appraisal of novelty. Predictability and controllability are central to several models of anxiety (Barlow, 2000; Foa, Zinbarg, and Rothbaum, 1992; Mineka and Kihlstrom, 1978) and are linked with differences in the orienting response and individual information processing 'styles'. For instance, when an aversive event is predictable (i.e. exposure with warning signal) this leads to acute anticipatory anxiety as the individual awaits the predicted outcome. However, when an aversive event is unpredictable (i.e. aversive event but no warning signal) the individual is in a constant state of alertness, which can lead to long-term sensitisation or chronic anxiety. The unpredictability of aversive stimuli can occur in two ways. First, the threatened individual is unable to reliably recognise premonitory signals or believes they are not present. These individuals thus under-predict aversive events and are considered to have a histrionic or 'hysterical' information processing style, characterised by hypovigilance, distractibility and difficulties distinguishing targeted from non-targeted stimuli. Second, the premonitory signals are perceived as continuously present and the individual remains highly vigilant and therefore sensitive to predicting danger. These individuals over-predict aversive events and are considered to have an 'obsessional' information processing style, characterised by hypervigilance and extreme sensitivity to potential dangers. Both processing styles are associated with an unreliable appraisal of threat, and can lead to chronic anxiety (Cloninger, 1986).

Cloninger, (1986) summised that novel stimuli elicit orienting responses in which the individual becomes more vigilant and alert. In other words, individuals with histrionic cognitive patterns tend to seek novelty, as it is adaptive for them, e.g. it increases their perceptual sensitivity and vigilance (Ludwig, 1972), which is consistent with Cloniger's theory. Conversely, individuals with obsessional cognitive patterns tend to avoid novelty because exposure to unfamiliar settings and stimuli is considered maladaptive. In contrast, they seek routine and familiarity, which is adaptive by reducing vigilance. One criticism of Cloninger's (1986) theory however, is that it could equally be argued that a negative experience following the under-predicting of aversive events may make the individual more alert, vigilant and anxious, which appears counter-intuitive to them actively seeking novel or unexpected events. Furthermore if a histrionic personality style is characterised by hypovigilance, the orienting response to novel events in these individuals might not be typical.

One of the most enduring models of personality traits associated with anxiety was that published by Eysenck, (1967). Like Cloninger, (1986) he described two main personality dimensions in this case labelled: neuroticism-stability and introversion-extraversion, with neurotic-unstable being indicative of an anxious personality. Eysenck believed these dimensions to be free of variation and statistical correlation, thus relatively 'pure' personality traits that may be found across cultures and ages. The personality traits described by Eysenck (1967) were influential, but have not gone unchallenged. For Gray (1983) the neuroticism and introversion dimensions in Eysenck's model were unstable and open to manipulation, as they could be altered with use of anxiolytics (suggesting to Gray that they did not represent stable

traits). Gray proposed two alternative personality dimensions, which he labelled 'anxiety' and 'impulsivity'. According to this model, the anxiety dimension reflected variation in a central 'Behavioural Inhibition System' (BIS), which maintains passive avoidant behaviour in response to punishment, non-reward and, importantly, novelty. The impulsivity dimension is thought to reflect variation in a central 'Behavioural Activation System' (BAS), which is responsive to cues signalling reward or escape from punishment and the activation of reward-seeking behaviour and aggression (Gray, 1982).

Gray's model implies that individuals who score highly on either or both of these dimensions will be susceptible to chronic anxiety ('neurotic' or 'unstable' according to Eysenck (1967), and 'harm avoidant' by Cloninger, (1986); although these authors did not make these direct comparisons themselves). Cloninger (1986) suggested that 'harm avoidance' involved a neurobiological tendency to learn to avoid punishment, non-reward and novelty. These individuals were deemed to have a temperamental construct that caused them to react to both social and non-social novelty with inhibition. Conversely, those individuals on the impulsivity or 'novelty seeking' dimensions were deemed to be exploratory, active and intensely attracted to novelty, and thus uninhibited in their approach to the unfamiliar. This provides support for the variation in novelty processing and its influence on the individual outlined previously.

In summary, the development of novelty-processing is a particularly important aspect of childhood. Novelty-preference has been viewed as highly adaptive and positive and is suggested to underlie intellectual development (Berg and Sternberg,

1985). At the same time the development of anxiety towards the strange or unfamiliar is also a normal part of childhood (Bowlby, 1969). Clearly the child must navigate an optimal course between these competing demands of novelty-preference and fear-of-the-unfamiliar in order to develop well-adjusted personality traits, and in order to become a cognitively-able adult. There is reason to believe that if this course is abnormal emotional problems and/or cognitive deficits may result. In support, the consistent avoidance of novelty and the unfamiliar has been linked to lower cognitive abilities in children and adolescents (Berg and Sternberg, 1985; Rose et al., 1986), but also to physiological differences (Kagan et al., 1987, 1988a), poor affective functioning (Eaves et al., 2004), and susceptibility to developing an anxiety disorder in later life (Biederman et al., 1993; Rosenbaum et al., 1991a,b; Schwartz et al., 1999; Van Ameringen et al., 1998). Indeed, the manner in which an individual responds to novelty bears some relation to those personality traits suggested to be indicative of anxiety in adults.

2.1. Anxiety Disorders in Children

Investigations into anxiety have focused primarily on adult populations, yet many cases of anxiety first develop during early to mid-adolescence (Strauss, Last and Hersen, 1998), with anxiety being one of the most prevalent forms of psychopathology affecting approximately 20% of children and adolescents at some point in their lives (Cohen et al., 1993; Shaffer et al., 1995). Although previous research indicates that many anxiety disorders are transient and resolve without intervention within 3 to 4 years (Last, Perrin, Hersen, and Kazdin, 1996; Pine, Cohen, Gurley, Brook, and Ma 1998), there is also evidence to suggest that in some cases anxiety remains stable across childhood and adolescence (Aksan and

Kochanska, 2004; Schwartz et al., 1999, 2003; Ialongo, Edelsohn, Werthamer-Larsson, Crockett, and Kellam, 1995), and can follow a chronic pathway into adulthood (Pine et al., 1998; Silove et al., 1995). Moreover, anxiety during adolescence is associated with up to a three-fold increase in risk for anxiety in adulthood (Pine at al., 1998), and among children there is high co-morbidity between anxiety and depression, which has been linked to an increase in severity of anxiety symptoms (Brady and Kendall, 1992). There is also evidence to suggest a familial component involved in the pathogenesis of childhood anxiety disorders, although the specificity of this relationship varies among individual anxiety disorders (Last, Hersen, Kazdin, Orvaschel, and Perrin, 1991).

Cognitive theory (e.g., Beck, 1976; Williams, Watts, MacLeod, and Mathews, 1988; 1997) and empirical research has demonstrated the presence of cognitive or information processing biases towards threatening stimuli in clinically anxious (Bradley, Mogg, White, Groom, and de Bono, 1999; MacLeod and Matthews, 1991; Mogg, Matthews and Eysenck, 1992; Mogg, Millar and Bradley, 2000; Taghavi, Moradi, Neshat-Doost, Yule and Dalgleish, 2000; Williams, Watts, MacLeod, and Mathews, 1997) and trait anxious (MacLeod and Matthews, 1988; Mogg, Bradley, and Hallowell, 1994) adults and children, and explicit memory bias for negative or critical faces in adults with social phobia (Foa, Gilboa-Schechtman, Amir, and Freshman, 2000; Lundh and Ost, 1996). These information-processing biases are proposed to operate throughout several aspects of cognition and to cause (MacLeod, Rutherford, Campbell, Ebsworthy, and Holker, 2002) or maintain (Mogg and Bradley, 1998) anxiety levels. In addition, it is proposed that biases associated with

threat are specific to anxious, but not depressed affect in adults and children (Beck and Clark, 1988).

Paediatric anxiety disorders are often associated with conduct disorders and antisocial behaviour (Eaves et al., 2004; Walker et al., 1991), and are linked with the onset of serious and debilitating co-morbid conditions such as substance abuse disorders, depression and suicidality (Achenbach, Howell, McConaughy, and Stangor, 1995; Pine et al., 1998). It is therefore unsurprising that there is emphasis on the importance of diagnosing paediatric anxiety disorders early, and particularly on the identification of the risk characteristics that make some children vulnerable, because these characteristics may predispose the child to adult mental health disorders (Milham, 2005).

2.2. Behavioural Inhibition: a personality trait associated with vulnerability to anxiety disorder in childhood.

One personality characteristic associated with anxiety that has received a lot of attention in children is that of behavioural inhibition. Links between an inhibited temperament and susceptibility for developing anxiety and anxiety related disorders is well documented (Kagan et al., 1988a; Rosenbaum et al., 1991a, 1991b; Biederman et al., 1990, 1993; Ameringen et al., 1998; Schwartz et al., 1999; McNaughton and Gray, 2000; Isolan et al., 2005). Behavioural inhibition, which is estimated to be present in 10 to 15% of children, is characterised by social withdrawal, as well as physiological factors such as an increase in salivary cortisol level, heart rate and papillary dilation when faced with novel situations or events (Kagan, Reznick, Clarke, Snidman, and Garcia-Coll, 1984; Kagan et al., 1988a;

Rosenbaum, Biederman, and Gersten, 1989). From a neurological perspective, a behaviourally inhibited temperament is believed to reflect a lower threshold to limbic excitability and sympathetic activation; hence increased reactivity of the amygdala and its projections to the striatum, hypothalamus, sympathetic chain and cardiovascular system (Kagan et al., 1988a).

Studies have shown that behavioural inhibition is identifiable in childhood as early as the second year of life (Garcia-Coll, Kagan, and Reznick, 1984; Kagan et al., 1984), and that behaviourally inhibited infants exhibit a delayed and wary approach towards toys that are unfamiliar and novel (Rothbart, 1988). Further studies suggested that children who remained inhibited throughout childhood were at increased risk of developing an anxiety disorder compared with those children who were not persistently inhibited (Hirshfeld et al., 1992). For example, a three-year follow-up of children aged two to seven years old with and without behavioural inhibition indicated that inhibited children were at a high risk for developing childhood onset anxiety disorders, and suggested that behavioural inhibition was a predictor of anxiety disorder later on in life (Biederman et al., 1993).

Due to its importance, the basis for this conclusion should be explored in greater detail. Some of these studies (e.g. Biederman et al., 1990; Hirshfeld et al., 1992) have relied on small samples (e.g. n = 30 (two groups): Biederman et al., 1990; n = 31 (three groups): Hirshfeld et al., 1992). Moreover, many do not assess the child directly (relying on parental report) and do not investigate children longitudinally. Furthermore, a study by Caspi and Silva (1995) produced conflicting results. Although these authors studied a longer interval (from age three to eighteen years

old) and had a large sample (n = > 800) they did not find that inhibited children were at increased risk for anxiety disorders in adulthood. This finding may have been due to the fact that their study was focusing on the links between behavioural style in childhood and adult personality traits, rather than risk for anxiety disorder per se. However, given the size and breadth of this study, it would be reasonable to expect that a proportion of participants who were categorised as inhibited may have developed (or been at risk of) clinically significant anxiety. Evidence from longitudinal studies suggests that inhibitory characteristics remain stable across infancy to pre-school years (Aksan and Kochanska, 2004; Kagan et al., 1984), and from the second year of life into adolescence (Schwartz et al., 1999). There is also longitudinal data that extends into adulthood, showing that a behaviourally inhibited temperament in childhood is associated with the development of an anxiety disorder in adulthood (Isolan et al., 2005). In conclusion, the evidence is mainly supportive of a link between the presence of stable behavioural inhibition in childhood and of the development of an anxiety disorder.

2.2.1 Environmental factors associated with behavioural inhibition

The environment in which the child is raised has been argued to play an important role in linking temperament and later adjustment (Thomas and Chess, 1977), and implicates parenting style as a contributory factor in the development of anxiety in children (Goldin, 1969; Parker, 1990). Sensitive parenting, defined as sensitivity to an infant's signals and mutual regulation between parent and child, has been demonstrated to contribute to the child mastering his or her own behaviour (Shaw, Keenan and Vondra, 1994) whereas intrusive parenting, defined as failing to modulate the pace of interaction with the child and forceful behaviour, may

interfere in the child's ability to self-regulate their behaviour (Calkins, Hungerford, and Dedmon 2004), leaving the child more vulnerable to underlying reactive tendencies such as extreme externalising behaviours. Studies have also investigated the interaction of parent behaviour and behavioural inhibition in the child, reporting stability and consistency in the association between shyness and behavioural inhibition at two years (Rubin, Burgess and Hastings, 2002) and later at four years of age (Rubin, Hastings, Stewart, Henderson, and Chen, 1997) in children whose mothers exhibited a controlling or derisive parenting style.

Non-parental care has also been shown to affect the relationship between parenting style and behavioural inhibition. Fox and colleagues (Fox et al., 2001) found that infants who displayed high negative emotionality at four months of age became less inhibited as toddlers when they were placed in non-parental care-giving environments such as day nurseries. This finding may be due to over-controlling parenting at home, compared with parenting that promotes independence, socialisation and perhaps exploration, as found in day-care (Fox, Henderson, Marshall, Nichols, and Ghera, 2005). Indeed, it may be the case that children who are cared for away from the home are more experienced in interacting with novel stimuli such as unfamiliar adults, peers and objects, which may improve underlying reactive traits (Perex-Edgar and Fox, 2005).

2.2.2. The role of parental psychopathology in relation to behavioural inhibition.

Studies assessing familiar patterns in adults with anxiety disorders have described an association between behavioural inhibition and anxiety disorders in childhood,

and adulthood psychopathology (Pollack and Smoller, 1995). A high rate of anxiety disorders in the offspring of adults with anxiety disorders has been described (Lieb et al., 2000; Mancini, Ameringen, Szatmari, Fugere, and Boyle, 1996; Biederman et al., 2001b) with Mancini and colleagues reporting that 49% of children in their study had at least one lifetime anxiety disorder diagnosis. Studies have also reported a link between anxious parents and inhibited offspring (Last, Phillips, and Statfeld, 1987; Last et al., 1991). Rosenbaum and colleagues (1991a) found that children whose parents have a diagnosis of panic disorder/agoraphobia (with or without major depression) were reported to present with significantly higher rates of behavioural inhibition than children from a clinical comparison group (i.e. had no parent with either panic disorders or depression). Furthermore, they found that parents of children with behavioural inhibition showed higher rates of anxiety disorders compared to parents of children without behavioural inhibition, thus suggesting that behavioural inhibition is linked to a familial predisposition to anxiety disorders (Rosenbaum, 1991b). One concern with the former study (Rosenbaum et al., 1991a) however is the use of psychiatric comparison groups rather than normal controls. Although it clearly states that the parents did not have panic disorder or depression, the authors failed to clarify the nature of the psychiatric disorders, which may have had a genetic or environmental influence on their offspring. The use of a normal control group may have been more effective in providing normative data by which to contrast rates of behavioural inhibition in children of parents with panic disorder/agoraphobia.

These data provide evidence for the role of environmental (e.g. parenting) factors in the development of childhood personality traits associated with anxiety; the

evidence for genetic susceptibility is indirect. Notwithstanding the role of environmental and/or parenting factors in the devlopment and maintenance of anxiety, a disposition for uncertainty to unfamiliar or novel events and situations can manifest from early childhood, perhaps shaping the development of personality, and in extreme cases leading to an anxiety disorder. To accept this possibility is to accept that behavioural inhibition is an early reflection of susceptibility to anxiety. This is a fundamental tenet of Gray's hypothesis of a highly reactive "behavioural inhibition system" (Gray, 1982). Understanding the role of behavioural inhibition may therefore be imperative if one is to investigate the links between normal variations in childhood anxiety and the appraisal of novelty.

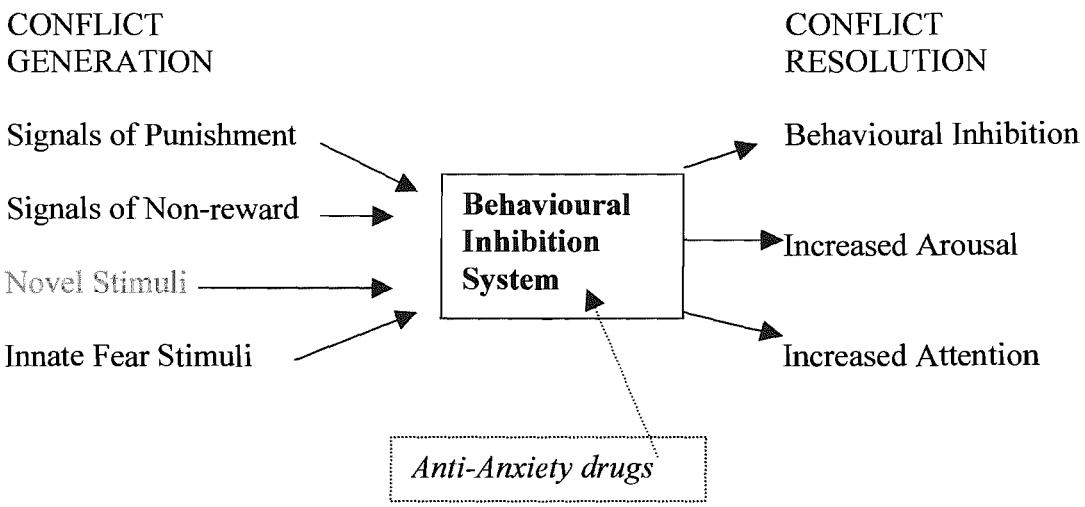
2.2.3. The Behavioural Inhibition System (BIS) Model

This model, proposed by Gray, (1982; McNaughton and Gray, 2000) represents one of the most comprehensive theories linking neurological and personality systems underpinning anxiety. The comparator model first postulated by Gray (1982) was originally developed as a theory of anxiety. It aimed to provide a basis for investigating those factors associated with the development and maintenance of anxiety, by proposing three interlinked levels of analysis: behavioural, neural processes and cognition (i.e. information-processing).

At the behavioural level this theory postulates the "behavioural inhibition system" (BIS) - to which reference has already been made. The BIS is defined by inputs associated with conflict generation, such as punishment and fear signals, and outputs associated with conflict resolution such as arousal and behavioural inhibition (see Figure 1). More specifically, the critical eliciting stimuli for

activating the BIS are those that may generate conflict, e.g. between new information and existing schema, such as the occurrence of punishment, omission or termination of reward ("frustrative nonreward"; Amsel, 1962) and novel stimuli. The resulting behaviour elicited by any of these stimuli is behavioural inhibition: increased level of arousal and orientation of attention – preparation for 'fight or flight'. Any of the three inputs to the BIS will elicit these outputs, unless - according to Gray (1982) - counteracted by anti-anxiety drugs (e.g. benzodiazepines) or brain lesions (e.g. to the Medial Prefrontal Coretx (MFRC) or Septo-Hippocampal System (SHS).

Figure 1: The Behavioural Inhibition System postulated by Gray (1982). This system is hypothesised to be activated by each of the classes of conflict-generating stimuli on the left-side and to produce each of the outputs on the right-side. Anti-anxiety drugs are thought to act specifically on the Behavioural Inhibition System (Re-drawn from Gray and McNaughton, 2000, with permission – see Appendix 1).



2.2.3.1. Neurological structures associated with the BIS model

It is important to first point out that there is no direct evidence to support a one-to-one relation between aspects of the BIS model and structures of the brain. There is, however, some support for a neurological underpinning to the model.

Gray proposed that from a neurological perspective, the set of neurological structures mediating the functions of the BIS are the septohippocampal system (SHS), originally referred to as part of the "Papez loop": areas of the temporal and frontal neocortex and the ascending serotonergic and noradrenergic pathways innervating these forebrain regions (Gray, 1982). Furthermore, Gray (1983) reported a substantial similarity between the profile of behavioural changes in animals following septal hippocampal lesions and that in humans following administration of anxiolytic substances known to decrease subjective anxiety (see Gray, 1982; Gray and McNaughton, 2000 for a review), suggesting that the anti-anxiety drugs acted on the SHS in order to produce the anti-anxiety effects. Recent animal studies, although limited, provide some support for this proposal with lesions of the SHS and related areas producing behavioural effects indicative of reduced anxiety and inhibition, further suggesting that these areas are overactive (e.g. Degroot and Treit, 2004; Menard and Treit, 1996; Shah and Treit, 2003). However, a study by McNish and colleagues (McNish, Gewirtz and Davis, 1997) found that lesions of the dorsal hippocampus in rats attenuated contextual freezing, but had no effect on fear-potentiated startle. This finding suggests that although the hippocampus may be involved in the mediation of anxiety, its exact role is unclear, as it does not appear to be critical for contextual fear conditioning.

Thus the majority of evidence for a biological association with Gray's model rests on those data showing an action of anxiolytics on the SHS and hence the BIS (Gray, 1982; McNaughton and Gray, 2000). The behavioural responses modified by administration of anxiolytic drugs have been described as features of the BIS model (Figure 1), and the mechanism by which the anxiolytic drugs modify 'BIS' behaviours as reflecting the control of 'theta activity' (rhythmical bursts of cell firing) in the SHS. Importantly, Gray acknowledged that the SHS, whilst central to his theory, was only one system in a complex set of neural networks which contribute to different aspects of anxiety and that it was this interaction with other structures (such as the cortex) that determined the changes in behaviour. Moreover, the proposed function of the SHS was not solely to control anxiety but to act as a simple comparator of inputs (Gray, 1982; McNaughton and Gray, 2000).

In support, according to Gray's theory, the SHS is associated with both the 'generation of predictions' and the comparison between these and actual events. When an unfamiliar or novel event occurs, there is a mismatch between expected and actual events. This causes the comparator to interrupt the current motor programme (inhibit behaviour), enabling future behaviour to be executed more slowly and carefully (increased vigilence/hyperarousal), and perhaps facilitate attempts to resolve the cause of the mismatch and also update existing knowledge schemas. While, this suggests a central role for the SHS in the expression of anxiety, there are few empirical data to support this assumption.

2.3 Approaches to the Neurobiology of Paediatric Anxiety Disorders

Over the past decade there has been an abundance of research investigating the neuroanatomy of anxiety and other emotional disorders in adults. However few studies have examined the neurobiological underpinnings of these conditions in children. It has been suggested that this limitation of the literature is due to a combination of high co-morbidity and strong diagnostic overlap among anxiety disorders (Vasa and Pine, 2004). In order to address this limitation, one approach has been to clarify and classify those pathophysiological factors associated specifically with anxiety (Vasa and Pine, 2004). These authors proposed a hierarchy of pathophysiological factors proposed to underlie anxiety disorders. These included the functional aspects of neural networks (e.g. demonstrated through neuroscience techniques: ERP recording/MRI fMRI), cognitive or physiological factors that were subserved by these neural networks, behavioural tendencies (e.g. behavioural inhibition) and anxiety symptoms. An example of authors demonstrating use of the hierarchical approach can be found in studies where associations have been made between the aforementioned pathophysiological factors. Gray (1982) theorised as to the functional aspects of neural networks that underlie anxiety disorders; Kagan and colleagues (1987) provided links between physiological factors such as increased heart rate and temperamental traits such as behavioural inhibition, and similarly, Biederman et al., (2001a) established a connection between behavioural inhibition and social anxiety disorder. Thus, this approach may be useful in clarifying the pathophysiological factors associated with anxiety through identifying the cognitive or physiological mechanisms that distinguish the anxious from the non-anxious child, and the neural circuits underlying them.

3. Brain-behavioural studies of anxiety

Early studies investigated systemic physiological responses associated with anxiety, such as the galvanic skin response. A complimentary line of evidence was gained through lesions studies, although the majority of these studies involved animals, making direct comparisons with human behaviour problematic. More recently, neuroscientists have begun to apply neuroimaging techniques (e.g. magnetic resonance imaging – MRI and fMRI) to investigate the involvement of those structures widely believed to be associated with anxiety (e.g. SHS, amygdala).

3.1. Physiological Studies

Lader and Wing, (1964) compared the galvanic skin response (GSR) associated with presentation of auditory stimuli (tones) in 20 adults (aged 19-53 years) with anxiety disorders and 20 matched controls, and found that the anxious group exhibited smaller responses to initial stimulus presentation than controls, but in general had higher basal GSR level and slower rates of habituation. A later study conducted by Hart, (1974) using simple auditory stimuli of varying intensities found that non-anxious individuals showed an initial heart rate deceleration which habituated over trials, whereas the anxious group did not show the same heart rate change and failed to habituate. Further suggestions of a physiological abnormality in anxious individuals was investigated by Cook and colleagues, (Cook, Melamed, Cuthbert, McNeil, and Lang, 1988). Using an imagery task, these authors looked at the diagnostic differences in the psychophysiology of emotional imagery. These authors found significantly larger heart rate and skin conductance increases in simple phobics and social phobics, compared with individuals with agoraphobia. This study concluded that there were important differences between diagnoses in

the organisation and content of phobic memories. However, the absence of a control comparison group in this study, made it difficult to provide support for a physiological abnormality between anxious and non-anxious individuals, despite the findings of previous studies.

More recent studies investigating physiological processes involved in anxiety have revealed considerable variation across individuals, and that such responses may be influenced by personality traits, such as inhibition and introversion, (Hamann and Canli, 2004). In support, personality traits have been found to influence the orienting response to affective auditory stimuli (Martin-Soelch et al., 2005). In this study a variety of physiological measures were used (e.g. heart rate, skin conductance, zygomatic muscle activity) to record subjects' responses to pleasant, unpleasant and neutral sounds. The authors concluded that the measure of personality trait anxiety increased the orienting reaction to all the sounds presented. These findings serve to strengthen the view that personality dimensions are involved in the onset and maintenance of anxiety disorders, and that such traits may manifest in altered physiology. However, these data do not provide direct evidence of brain-behavioural associations.

3.2 Lesion Studies

In support of earlier theory (e.g. LeDoux, 1995, 1998, 2000), animal lesion studies have implicated the amygdala in the mediation of emotional and social behaviours. More specifically, the amygdala has been implicated in the detection and avoidance of danger, and in the inhibition of approach to novelty (Amaral, 2002). The amygdala is composed of multiple nuclei that subserve various functions (Davis

1992; LeDoux, 1998). Located within the anterior temporal lobe of both the human and nonhuman primate brain (Amarel, Price, Pitkanen, and Carmichael, 1992), this structure is well connected to send information to the ventral frontal lobes, hippocampus, thalamus and hypothalamus (see Figure 2), and is suggested to play an important role in the behavioural and cognitive aspects of the fear response (Davis, 2000; LeDoux, 1995, 2000), fear conditioning (Bechara et al., 1995; Davis 1998; LaBar, LeDoux, Spencer, and Phelps, 1995; LeDoux 1998), behavioural inhibition (Kagan et al., 1988a), and response to novelty (Amaral 2002; Schwartz, Wright, Shin, Kagan, and Rauch, 2003). It has also been found to relate more strongly to social/interpersonal than non-social dimensions of anxiety (Killgore and Yurgelun-Todd, 2005).

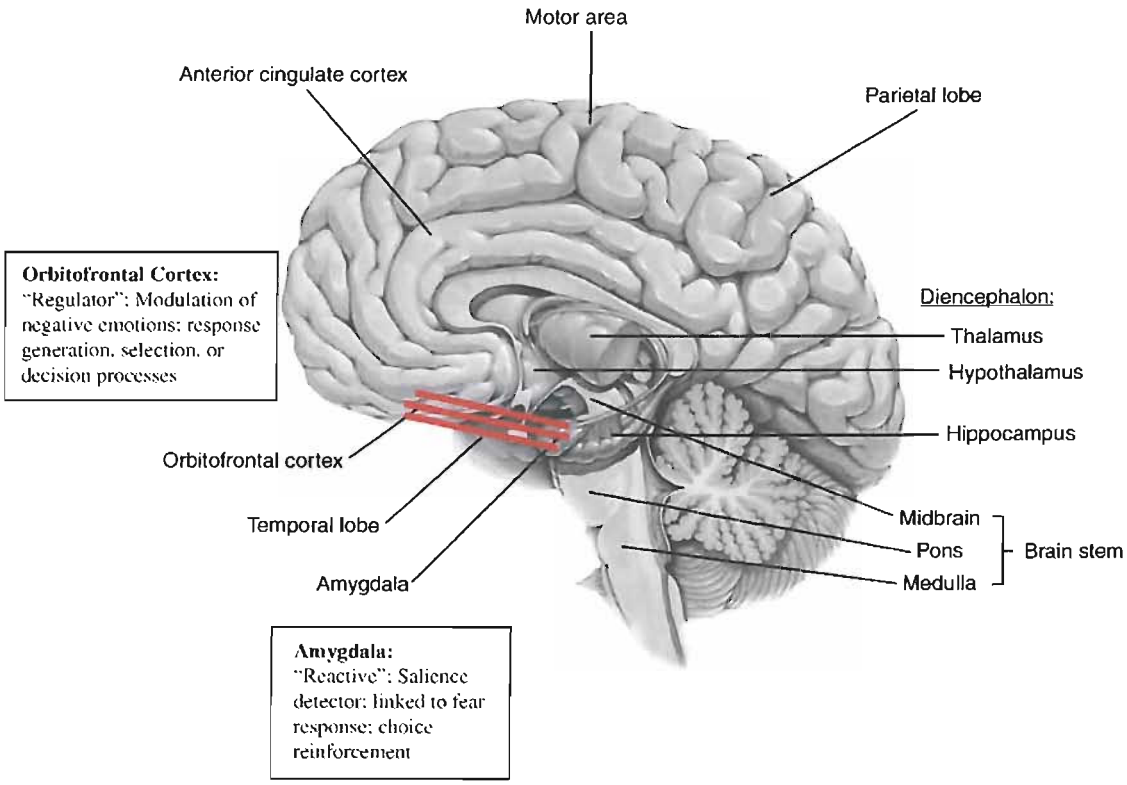


Figure 2. Location of the amygdala in the human brain and the reciprocal connections between the amygdala and the orbitofrontal cortex (red bars). (Copied with permission from Perez-Edgar and Fox, 2005 - see Appendix 2).

Early studies involving lesions of the amygdala in non-human primates frequently reported that the amygdala has an influence on social behaviour. Rosvold and colleagues (Rosvold, Mirsky and Primbram, 1954) reported two out of the three lesioned animals in their study to be less dominant in a group situation and more aggressive when on their own. However they attributed some of these changes in behaviour to the animal's social environment, whilst also acknowledging that the behavioural differences were consistent with damage to the amygdala. Another study reported different effects on social behaviour, with the lesioned animals showing social indifference, failure to display appropriate aggressive and submissive gestures and rejection from their social group. The authors of this study also suggested that both the size of lesion and the age at operation were major factors in determining the degree of behavioural change, with larger lesions and older age producing more prominent behavioural changes (Dicks, Myers and Kling, 1968). However, more recent criticism of these studies has highlighted the non-specificity of destructive techniques used during the removal of the amygdala (e.g. suction ablation) (Amaral, 2002; 2003). These techniques destroyed or damaged not only the cell bodies in the lesioned nucleus, but also those axons that travel through the amygdala and neighbouring brain regions (e.g. perirhinal cortex required for visual processing; Buckley and Gaffan, 1997). For this reason, any comparison between amygdala function and behaviour based on these early studies should be reviewed with caution. Furthermore, behavioural data was based on description and thus, subjective, resulting in data that could not be analysed statistically. More recent studies (e.g. Amaral, 2002, 2003) have attempted to overcome these difficulties through the use of more refined techniques (e.g. selective neurotoxins injected into the brain), which destroy only selective cells,

leaving surrounding fibres and brain regions intact (Jarrard, 2002). Furthermore, converging evidence of lesion specificity may now be provided by MRI, and behaviour defined using more rigorous methodology and scoring criterion, thus providing more objective evidence (Amaral, 2003). These more recent studies are described in greater detail.

Amygdala lesions in both humans and animals produce deficits in fear conditioning (Amaral 2002; Davis 1998; De Bellis et al., 2000; LaBar et al., 1995) and altered social interaction (Emery, Capitanio, and Mason, 2001). A study by Amaral, (2003) found that mature rhesus monkeys with bilateral lesions of the amygdala engaged in uninhibited species typical social behaviour (e.g. grooming, play, facial expressions), and demonstrated a lack of concern about normally fear-inducing stimuli, such as a snake. Bilateral damage to the amygdala therefore appeared to result in reduced fear and greater emotional response. Similar findings were reported in infant monkeys that received bilateral lesions of the amygdala at two weeks of age, but who were reared by their biological mothers (Amaral, 2003). Social interaction with their mother was comparable to that seen in non-lesioned controls, however they demonstrated more fear (e.g. increased fear expression: fear grimaces, screams and less social interaction) when placed into novel social situations, yet at the same time also showed increased social interest. This suggests that part of their difficulty lay in the evaluation of novelty. Amaral concluded that the amygdala is not necessary for species typical social behaviour or for gaining social knowledge during development, but that it is a critical component of a system that evaluates the environment for potential dangers. It may therefore have a modulatory role in social behaviour, perhaps associated with the inhibition of social

interaction in novel environments while the potential threat is being evaluated (Amaral, 2003).

Studies involving humans with amygdala damage are rare. Those that have been published describe impaired judgement of negative facial expression, and poor judgement of trustworthiness (Adolphs, Tranel, Damasio, and Damasio, 1994; Adolphs, Tranel and Damasio, 1998), as well as impaired recognition of fear in others (Adolphs et al., 1999). However, it is important to note that many of the patients involved in these studies had extensive damage to brain regions extending beyond the amygdala, typically as a result of very rare diseases: Urbach-Wiethe disease, which also damages the anterior entorhinal cortex (Adolphs et al., 1998); surgical temporal lobectomy which typically involves the hippocampus and surrounding temporal cortices (Adolphs et al., 1998); and encephalitis which can cause substantial damage to the brain in general (Adolphs et al., 1999). It is therefore unclear as to whether the impairments reported in these individuals were due to the amygdala or to abnormalities in neighbouring brain regions (e.g. the hippocampus), or to more distal brain regions, that were affected by the loss of amygdala connectivity.

Damage to the amygdala and its cortical connections has also been linked to a cluster of behavioural changes known as Kluver-Bucy Syndrome (KBS: Kluver and Bucy, 1939). Originally noted after bilateral removal of the anterior temporal lobes in primates (Kluver and Bucy, 1939), the existence of KBS in humans, although rare is documented (Hayman, Rexer, Pavol, Strite and Meyers, 1998; Lilly, Cummings, Benson, and Frankel, 1983; Trimble, Mendez, and Cummings, 1997 for

a review)). Similar to the clinical descriptions of Adolph and colleagues (1994, 1998, 1999), the KBS presentation includes the inability to recognise the emotional significance of objects; altered emotional behaviour, particularly placidity and the tendency to react to every visual stimulus and memory deficits. Thus, the behavioural changes described could be due to the removal of the amygdala, but may also be due to damage caused to more widespread brain areas.

In summary, the amygdala has been implicated in fear and novelty processing, and indirectly with anxiety in animal lesion studies, and in some human disorders. Amygdala dysfunction is also associated with psychopathology in the absence of overt brain abnormality, e.g. depression (Drevets, 2000) and autism (Baron-Cohen et al., 2000), as well as social anxiety (Birbaumer et al., 1998) and paediatric anxiety disorders (Thomas et al., 2001).

3.3 Magnetic Resonance Imaging (MRI) and fMRI

Magnetic resonance imaging (MRI) studies, and, more specifically, functional MRI (fMRI), allows for the direct comparison of structural-functional relationships in healthy individuals, and in those with psychopathology. In particular, fMRI permits the investigation of brain function associated with the processing of potentially anxiety-eliciting stimuli in children, in whom there are few if any lesion studies.

With regard to fMRI studies, face processing has been a particular focus of interest, revealing increased amygdala activation associated with fearful compared to neutral or happy faces in normal adults (Breiter et al., 1996; Morris et al., 1998; Killgore, Oki, and Yurgelun-Todd, 2001), and in association with fearful faces in children

(Baird et al., 1999). This finding was also replicated in a study by Thomas et al., (2001) where anxious children exhibited greater responses to fearful as opposed to neutral faces. However, a study by Pine and colleagues (2001) failed to engage the amygdala in either healthy adolescents or adults. This difference may be accounted for by methodological factors, such as subtle differences in paradigm and the nature of the stimuli, but indicates that the evidence for amygdala involvement in anxiety-related cognitive processing is inconsistent.

Despite this uncertainty, quantitative MRI studies examining the structure of brain regions in children with anxiety disorders have demonstrated amygdala abnormality. Significant gray matter volume decrease has been reported by one American group (Milham et al., 2005), while others have reported significantly *increased* amygdala volume (De Bellis et al., 2000). In one of these studies the effect of abnormal amygdala size was particularly marked on the left side (Milham et al., 2005). In support, studies of patients with amygdala lesions suggest that left-lateralised damage might exert particularly robust effects on the experience of emotions as found in anxiety disorders (Glascher and Adolphs, 2003). Others have suggested an association between childhood anxiety and depression (often associated with anxiety) and neurodevelopmental dysfunction in a neural circuit involving the amygdala (MacMillan et al., 2003).

It should be noted that few researchers would claim that the amygdala functions autonomously in processing fear and fear-related behaviours in animals and humans. This structure has projections to the superior temporal gyrus (STG), the thalamus and the pre-frontal cortex. Thus, it is more appropriate to view these brain

regions as comprising a concertedly working neural network underpinning the ability to interpret other's intentions, desires and beliefs (De Bellis et al., 2002), influence social intelligence (Brothers, 1990) and social information (Baron-Cohen et al., 1999). Indeed, in studies of experimental conditioning amygdala activity is thought to be modulated by inputs from the STG, which in turn is connected to other structures involved in higher cognitive processing of the fear experience (Quirk, Armony, and LeDoux, 1997). Quantitative MRI studies such as that reported by De Bellis et al., (2002) show that children with generalised anxiety disorder have significantly larger STG total and gray and white matter volumes than controls, with a right hemispheric dominance; a finding that is incompatible with others who have noted greater amygdala differences between anxious and non-anxious individuals on the left side (Milham et al., 2005). Conversely, several studies have demonstrated right-sided prefrontal activation in behaviourally inhibited children (Kagan and Snidman, 1999) who tend to be avoidant of situations that are novel (Kagan et al., 1987; Schwartz, 2003) and who are often predisposed to develop childhood anxiety disorders (Biederman et al., 1993).

Daffner and colleagues (2000) used electroencephalography (EEG) to demonstrate the central role of the prefrontal cortex in directing attention to novel events (Daffner et al., 2000), which may suggest that this area is over active in children who are behaviourally inhibited. However, other EEG studies have revealed conflicting results. Heller, (1997) found an asymmetry in favour of greater left hemisphere activity in anxious participants with self-reported anxious apprehension, but right parietal activity was greater during anxious arousal. Greater EEG activity in the right hemisphere of anxious adults has also been reported (e.g. Davidson,

Abercrombie, Nitschke, and Putnam, 1999). In addition, a positron emission tomography (PET) study also revealed healthy subjects with high trait anxiety to have greater right-left ratios of central metabolism than low trait anxiety subjects (Stapleton et al., 1997). Although in support of Heller, (1997), Davidson and colleagues reported greater posterior right-hemispheric activity in individuals with a high anxious arousal. It may therefore be concluded that the direction of hemispheric asymmetry may be dependent upon the type of anxiety being investigated and the methodology used to establish extent of anxiety.

In their quantitative MRI study, De Bellis, (2002) proposed that anxious children without a history of trauma have a propensity for larger right amygdala and STG volumes than non-anxious children, and that in turn this results in the development of those personality traits associated with risk of anxiety disorder. In other words, children predisposed to having abnormal right temporal lobe structures are more likely to be anxious. The basis for this speculation deserves consideration. While anxiety disorder may indeed result from brain abnormality, it is also the case that the brain may be shaped by chronic anxiety. In order to address this possibility longitudinal studies are required, beginning from infancy. One study is particularly important with regard to this issue. Schwartz et al., (2003) found amygdala hyperresponsiveness to novel faces in adults whose temperament was previously categorised as behaviourally inhibited during very early childhood. More specifically, brain function was studied in adults who had been categorised in the second year of life as inhibited and compared with those adults previously categorised as uninhibited. The 'early-inhibited' adults showed greater amygdala activation in response to novel versus familiar faces. It may therefore be the case

that those infants who show predispositional personality traits (e.g. behavioural inhibition) are at risk of maladaptive brain plasticity, particularly in those areas associated with anxiety, namely the STG and amygdala, and that this may increase the likelihood of anxiety disorder in later childhood. The time-period during which the brain may be sensitive to such modulation is not known, although evidence suggests that the brain is still developing until the child reaches early adulthood (Giedd et al., 1999; Giedd, 2004). This suggests that experiences can still modulate the development of both personality and the pattern of brain connectivity well into childhood. Perhaps it may be considered therefore, that children learn to be anxious, and that this emotional predisposition becomes as much a feature of their brain function at maturity as – for example – their ability to speak a second language. While such hypotheses are currently speculative, the advent of MRI and other neuroscience techniques permit the investigation of brain-behaviour relationships underpinning anxiety in greater detail. It is anticipated that the results of these studies may pave the way towards a greater understanding of the development and maintenance of childhood anxiety disorders than are currently available.

4. Event-Related Brain Potentials (ERPs)

Event-related brain potentials (ERPs) are neural responses associated with sensory and cognitive processes, with the former being automatic central nervous system responses to sensory stimuli, and the latter depending more on the conscious state of the individual and task instructions.

ERPs are recorded noninvasively at the scalp surface and do not necessarily require a motor or verbal response. This makes the technique particularly useful when working with children, who may be unable to describe accurately or be unaware of their responses, particularly those with an emotional loading. In particular, ERPs are time-locked to the presentation of a stimulus or a response offering excellent temporal resolution, and allowing an insight into early attentional processing (which may occur within a few hundred milliseconds of stimulus presentation): inferences can be made as to the speed at which the brain processes sensory information and how this is influenced by top-down attentional modulation, and bottom-up attentional capture.

At a neural level, ERPs reflect post-synaptic activity (brain electricity) that disperses towards the scalp. They reflect the summation of brain activity within a given region, but spatial resolution is limited. While the ERP technique is able to demonstrate gross laterality and anterior-posterior effects according to where the component is maximal, in general they do not indicate where in the brain activity is generated (i.e. this technique cannot confirm that activity is coming from the hippocampus as in fMRI). Spatial information may also be inferred based on other evidence, for instance, when a component is attenuated in someone with a hippocampal lesion, but not in someone with a parietal lobe lesion, as demonstrated in both human and animal studies (Knight, 1984, 1996, 1997; Amaral, 2002, 2003), some research groups have also used MRI and ERP techniques in tandem in order to provide both spatial (fMRI) and temporal (ERP) information about brain response to certain stimuli.

The basic principle of this technique is that an ERP component is a brief epoch ('chunk') of the continuous EEG, time-locked to the presentation of a stimulus or to the occurrence of a motor response. Many trials of similar stimuli or responses must be obtained, as the signal from one trial alone is not strong enough to be detected against the background of EEG, and other noise (e.g. muscle artefact). A large number of ERP epochs centred on the same stimulus have to be averaged, in order to extract the ERP component from the underlying EEG. Once an ERP average has been obtained, the various components are described according to their polarity (P = positive and N = negative), and time of maximal appearance (e.g. 300ms $\Rightarrow$ P300; often abbreviated to P3). The amplitude and latency of such components may then be compared between groups (e.g. low and high trait anxious) and/or between stimuli (e.g. low and high tones).

4.1. ERP studies of novelty processing.

Some studies have specifically focused on ERP components associated with the processing of novel events (Cycowicz and Friedman, 1997; Friedman et al., 2001; Friedman and Simpson, 1994; Guerra, O'Donnell, Nestor, Gainski and McCarley, 2001). These have revealed that the orienting response elicited by unexpected (novel) events consists of a characteristic ERP pattern, composed in sequence of the N100 and the novelty P3 (Friedman et al, 2001). The mismatch negativity MMN has also been described. This component is observable in a 'difference waveform', obtained by subtracting the waveform from frequent events from that obtained from deviant events. Essentially the MMN overlaps the N1 and provides similar information.

The N1 is believed to reflect pre-attentive sensory-processing mechanisms occurring very early (e.g. within 200ms) and indicating the simple detection of a 'different' sound (e.g. see Näätänen, 1992 for review). Unexpected novel stimuli also elicit a subsequent P3 response that is also believed to be independent of attention and/or task relevance (Courchesne, Kilman, Galambos, and Lincoln, 1984; Friedman et al., 2001), but is associated more with the evaluation of those events in terms of determining whether or not the stimulus should elicit a behavioural response (e.g. "rapid processing of new or unexpected information that may have biological significance for survival - "*what is it*", and preparation to fight or flight" – A. Hogan, unpublished doctoral thesis, chapter 6, 2003). Due to the potential importance of these components for our understanding of novelty processing, they are now described in greater detail, in particular with regard to their presence in the ERP waveforms of children as well as adults. First, however, the novelty oddball paradigm - commonly used to elicit these ERP components - is described.

4.1.1. Novelty Oddball Paradigm

The target P3 and novelty P3 are typically elicited in novelty oddball paradigms, where deviant (e.g. high 'target' tones – low probability) and novel stimuli (e.g. novel noises – also low probability) are infrequently interspersed with standard stimuli (e.g. low tones – high probability). Participants are often required to push a button when they hear deviant (high tones), but not novel stimuli, which is why this type of stimuli is often referred to as 'target', i.e. this keeps the participant's attention focused on the task and at the same time provides a control for the possibility that the ERP changes are associated with lower probability rather than stimulus-novelty.

4.1.2. ERP components associated with novelty processing

Novel stimuli have been shown to invoke the orienting response, which is a shift in attention that enables an organism to respond quickly to a change in its environment, such as the occurrence of a novel sound (Sokolov, 1990). This response is seen as imperative to biological adaptation and survival and has been investigated in recent years in a series of studies in humans using ERPs in the auditory modality (Friedman and Simpson, 1994; Cycowicz and Friedman, 2004; Määttä et al., 2005a, 2005b).

Research with both adults and children as young as five years old has suggested that the frontal lobes are sensitive to the novelty of an event, whereas the parietal lobes are more active in the processing of pre-categorised target stimuli (e.g. low probability high tones embedded in a series of low tones – the 'target' P3; Cycowicz and Friedman, 1997; Daffner et al., 2000, 2003; Knight, 1984). At least two types of P3 are recorded in normal subjects in the auditory (Squires, Squires, and Hilliard, 1975; Knight, 1984), visual (Courchesne, Hilliard and Galambos 1975) and somatosensory modalities (Yamaguchi and Knight, 1991), with task relevant correctly detected target stimuli generating a parietal maximal P3 (Target P3), whereas non-target, unexpected and/or novel stimuli that require no behavioural response generating an earlier latency, frontocentral P3 (Novelty P3).

Studies have revealed that novel stimuli are associated with increased P3 amplitude over the frontal lobes compared to standard and deviant stimuli (Friedman and Simpson, 1994; Cycowicz and Friedman, 1997; Daffner et al., 2000, 2003). There is also evidence of a modulating role of age on ERP amplitude and scalp

distribution to target and novel events. Friedman and Simpson, (1994) found that younger adults' P3 scalp distribution shifted from a relatively frontal to a more posterior focus when novel stimuli were repeated. It has also been found that with event recurrence (Courchesne, 1978; Friedman and Simpson, 1994) and repetition (Cycowicz, Friedman, and Rothstein, 1996; Kazmerski and Friedman, 1995; Knight, 1984) this neural response habituates, leading to a generalised decrease in amplitude. In contrast, pre-categorised (deviant - target tones) are processed more posteriorly from the start and do not appear to habituate (Cycowicz and Friedman, 1997). The target P3 associated with this class of stimulus is therefore believed to represent a 'there it is' experience, whereas the novelty P3 reflects more the sensation of 'what was that?'. In summary, as an individual becomes more familiar with hearing novel noises, this class of stimuli becomes less unexpected and less novel, and thus the degree to which attention is diverted from the task of detecting target tones reduces.

Those components that come before the novelty P3 have been less well studied with regard to novel stimuli. In general, the N1 is a transient response to sound onsets and offsets and has multiple generators, most of them residing in the temporal lobe (Näätänen and Picton, 1987; Woods, 1995). Two recent studies investigating the processing of novel auditory events has shown the N1 component to be more prominent (longer latencies and larger amplitudes) in children compared to adults (Määttä et al., 2005a, 2005b). The N2 component is also implemented in stimulus comparison and is involved in discrimination between target and non-target stimuli (Oades, Dittman-Balcar, and Zerbin, 1997). Evidence suggests that in fact both N2

and P3 components reflect the awareness of the individual that an unexpected or novel event has occurred (Leppert, Goodin, and Aminoff, 2003).

A fundamental question that may be addressed by the standard oddball task (i.e. only standard and target stimuli) concerns the degree to which very early sensory processes may modulate attention. Some studies have explored this by instructing the individual to attend to different stimuli presented to different ears. Attending to tones has been shown to enhance auditory N1 amplitude and indicates that attentional modulation of the auditory ERP response can operate as early as 100ms ('N1') post-stimulus presentation in adults (Hillyard, Hink, Shwent, and Picton, 1973) and children (Määttä et al., 2005a, 2005b). More specifically, children have shown clear signs of selective attention as indicated by enhanced N1 amplitudes to attended stimuli (Berman and Friedman, 1995; Oades et al., 1997). The N1 is also suggested to reflect the orienting of attention towards task relevant stimuli (Luck, Heinze, Mangun, and Hillyard, 1990) and has been the earliest component to be reliably sensitive to manipulations of attention in the auditory domain. It should be noted that when novel stimuli are added to a standard oddball paradigm ('novelty auditory oddball') it is the convention not to inform the individual of their existence – hence they remain 'novel' and 'unexpected'. Thus, these types of stimuli may represent bottom-up capture or interruption of attention away from the task at hand, i.e. selectively attending to target tones. However, by applying an attention manipulation to the novelty auditory oddball task, Määttä et al., (2005a) reported that while in children, novelty-elicited N2 responses were larger to left ear stimuli irrespective of the direction of attention (i.e. ear in which they were instructed to listen out for target stimuli), adults displayed enhanced novelty elicited N2

amplitudes on the attended side. This suggests that unexpected novel stimuli may therefore elicit a greater response when in the context of attended stimuli when compared to unattended stimuli in adults but not in children. In general, it is believed that the P3 (and frontal N2) component reflects some level of awareness that an unexpected or novel event has occurred – i.e. attentional capture (Leppert et al., 2003), but the extent to which this is *conscious* awareness is not confirmed.

The evidence presented thus far indicates that ERP components associated with novelty processing may be recorded in children. Indeed, the brain mechanisms responsible for the processing of novel environmental information may be observed in infancy – although the components are not exactly the same as those seen in adults (Kushnerenko et al, 2002), further indicating that brain activity associated with novelty processing is essential to human adaptive functioning. More adult-like novelty ERP components are in place by the time children are at school age (Cycowicz and Friedman, 1997). These components may reflect the efficacy of the behavioural and physiological repertoire available to young children for dealing with novel situations, establishing links between seemingly different events, and forming the basis for new knowledge structures. Määttä et al., (2005a) investigated the processing of novel auditory events in children and adults and reported that the ERP waveforms elicited by complex, novel stimuli were similar between adults and children. There were reported differences however with the more frontally distributed P3 components, with the waveforms of adults comprising longer latency P3s at anterior sites and target P3s at posterior sites. In children however the target P3, like the novelty P3, was maximal at frontal sites. This may suggest a difference in processing behaviour between adults and children that reflect higher brain

function related to cognitive stimulus evaluation (e.g. categorising or labelling a stimulus). Given that the orienting to novel stimuli is a function known to be dependent of the frontal lobes (Daffner et al., 2000, 2003), and because the structural maturation of the frontal cortex shows that developmental courses are not completed until late adolescence (Giedd et al., 1999; Giedd, 2004; Huttenlocher, 1990), this difference in frontal lobe activity associated with novel-stimulus processing is perhaps unsurprising. Of interest was their finding that the N1 and N2 components elicited larger amplitudes in children than adults (Määttä, 2005b). This was explained by possible differences in orienting behaviour between adults and children, with adults requiring less effort and time than children, to process stimuli.

4.2 Brain lesions studies – evidence to suggest a neuroanatomy of novelty processing.

Evidence obtained from intracranial ERP investigations in patients with epilepsy (e.g. Halgren, Marinkovic, and Chauvel, 1998, for review), and in patients with localised brain lesions (e.g. Knight, 1984), converges with the scalp-recorded data obtained from typically developing populations (Knight, 1997) in suggesting a widespread neural network for novelty processing, in which the frontal lobes are an important component. In particular, a study by Knight, (1984) used an auditory novelty oddball task with adults with unilateral lesions of the dorsolateral prefrontal cortex, a region believed to play a significant role in orienting behaviour (Daffner et al., 2000). Results showed that the P3 components of the patients, relative to the controls, were markedly reduced at frontal scalp sites, but this was not the case for the P3 to target stimuli (Knight, 1984). Subsequent studies also involving patients with prefrontal lesions confirmed this observation (Daffner et al, 2000, 2003;

Knight, 1997) suggesting that the dorsolateral prefrontal cortex contributes significantly and preferentially to novelty P3 generation (Yamaguchi and Knight, 1991).

Additional neuroanatomical structures have also been demonstrated to contribute to the scalp-recorded novelty ERP response. Knight, Scabini, Woods, and Clayworth, (1989) showed that lesions of the lateral parietal lobe had no effect on the auditory P3 while lesions of the temporal-parietal junction eliminated the P3 at both frontal and posterior scalp sites. Subsequent lesion studies have shown the temporal-parietal junction to be critical for generating the scalp-recorded target and novelty P3s (Yamaguchi and Knight, 1991).

Previous studies involving lesions of the temporal-parietal junction have also revealed reduced auditory N1 amplitude, while lesions of the frontal cortex had no significant effect on this component (Knight, Hillyard, Woods and Neville, 1980, 1981). In a study employing a selective attention modulation, it was found that frontal brain lesions did alter the auditory N1, while the amplitude of components associated with the unattended ear remained unaffected (Knight et al., 1981). These studies demonstrate that early attentional ('top-down') modulation of sensory processing is possible.

In the 1996 study by Knight, lesions of the posterior hippocampal formation had a differential effect on novelty and target P3s. While, auditory, visual and somatosensory target P3s were unaffected, the novelty P3 was significantly reduced in all sensory modalities in hippocampal patients. This provides support for the

involvement of the temporal as well as the frontal lobes in the processing of novelty. Interestingly, the controls and not the patients produced phasic skin conductance responses to the novel events, suggesting the patients had a reduced somatic response when orienting to novel events, thus providing further evidence that ERP components reflect more general physiological response to novelty, perhaps in terms of the salience of such stimuli to the individual.

4.3 Modulation of ERP components by variation in personality

Studies investigating the P3 component have attempted to identify the moderating role of personality traits and more serious psychopathology, but these studies are few and far between. Personality traits of extraversion and introversion reportedly influence target P3 amplitude: in one study introversion was associated with larger P3 amplitudes, suggesting to the authors that introverts attended the to the task more than extroverts (Daruna, Karrer, and Rosen, 1985), whereas others have found the opposite, namely that the P3 amplitude was smaller in introverts than extroverts, (Cahill and Polich, 1992). Other studies investigating P3 amplitude in healthy subjects have found it to be positively related to a preference for novelty and negatively related to harm avoidance (Hansenne, 1999; Pierson, Houezec, Fossaert, Dubal and Jouvent, 1999). A more recent study identified a relationship between novelty P3 amplitude and broad personality dimensions in healthy individuals. Guerra and colleagues, (2001) used an auditory oddball paradigm with novel sounds to test for personality correlates of P3 amplitude and found that P3 amplitude was negatively related to neuroticism and positively related to extraversion, openness, agreeableness and conscientiousness. The overall findings from these studies

suggest that there may be ERP correlates of major personality traits, but the literature is currently limited.

4.4 Psychopathology and ERP components in adults

It has been claimed that ERPs are widely used to examine dysfunction of information processing in both psychiatric and psychological disorders (Munte and Kunkel, 1990; Timsit-Berthier, 2003; Tueting et al., 1984; Ullsperger and Gille, 1985 for a review). However, research into components such as the P3 comparing healthy individuals with psychological or psychiatric disorders also has its limitations. For example, at times the findings are inconsistent, and there are also methodological confounds such as the use of 'passive' and 'active' tasks which may limit comparisons (Nb. In an passive oddball task the individual is often allowed to read or watch silent cartoons, whereas in an active task they are required to respond to target tones). Notwithstanding these concerns, there is evidence for reduced target P3 amplitude in associations with psychopathology.

Increased P3 latency and reduced P3 amplitude have both been found in patients with borderline personality disorder and in those with schizophrenia (Kutcher, Blackwood, Clair, Gaskell, and Muir, 1987). A more recent study supports this finding, by demonstrating a reduction in P3 amplitude for both target and novel stimuli in participants with a diagnosis of schizophrenia (Kirino and Belger, 2004). Similar results have been found in patients with a diagnosis of antisocial personality disorder (Bauer, O'Connor, and Hesselbrook, 1994). Porjesz and Begleiter, (1998) investigated the auditory P3 in alcoholics and reported prolonged latency to attended auditory targets, however this was not the case for attended visual targets

or for unattended novel auditory stimuli. Such ERP studies are important in demonstrating the role of psychopathology in modulating brain response, and – importantly - suggest that such modulation is not specific to any disorder, but may indicate a generalised vulnerability to psychological and neural dysfunction.

Of particular interest for this review, however, is that the N1, N2 and P3 components have been shown to be influenced by anxiety in adults (Drake, Pakalnis, Phillips, Padamaden, and Hietter, 1991; Iwanami, Isono, Okajima, and Kamijima, 1997). Studies investigating the influence of anxiety and anxiety-related disorders have frequently reported differences in ERP components between anxious and non-anxious subjects. For example, studies of adults with panic disorder (PD) have revealed an alteration of early information processing in this subject group. Knott, Lapierre, Fraser, and Johnson, (1991) reported that N1 and N2 amplitudes for both target and non-target tones were significantly larger in the PD patients compared with controls. In a similar study using the auditory oddball task, PD patients exhibited larger N1 and N2 amplitudes than controls, although they did not differ significantly in P3 latency and amplitude (Iwanami et al., 1997). Recall that the N1 component may reflect synchronous activity of neurons that take part in filtering the relevant stimuli from the irrelevant stimuli at the pre-attentive learning stage (Näätänen, 1990). This suggests that anxiety may influence the alteration of very early information processing. Moreover, a study of ERPs in PD and generalized anxiety disorder (GAD) involving the analysis of inter-peak latencies (i.e. IPL: N1-P2, P2-N2 and N2-P3) concluded that attention-related processes in the cerebrum are actually accelerated (i.e. shorter ERP latencies) in PD patients (Hanatani et al., 2005). The authors suggests that patients with PD rapidly transmit

and process stimulus information filtered at the pre-attentive processing stage (N1) to the attentive processing stage (P2), whereas this process may be far slower in patients with GAD, as suggested by comparably longer latencies.

There is further conflicting evidence. In another study of adults with GAD inter-peak latencies were significantly longer in patients with anxiety compared to controls, with a reduction in N1 and P2 amplitudes being observed in the anxious group (Drake et al., 1991). A similar finding was reported in a study of cognitive function in social phobia, with patients showing reduced N1, N2 and P2 amplitudes and increased P3 latencies compared with controls (Sachs et al., 2004). This finding however was not replicated in a study of affective responses to threat involving subjects with specific phobias (Miltner et al., 2005). Results revealed significantly larger amplitudes of later ERP components (P3) but not of early components (N1, P2, N2) in phobic subjects when processing feared stimuli. This fear-associated increase of P3 amplitudes was maximal at centro-posterior brain sites. Furthermore, phobics, but not controls rated feared stimuli to be more negative and arousing than fear-relevant, emotional neutral and pleasant stimuli (Miltner et al., 2005). Fear conditioning research has documented that the 'fear response' is an automatically activated system when confronting threatening stimuli (LeDoux, 2000). Since later ERP components and arousal ratings were only significantly increased when phobic subjects were processing feared stimuli, P3 amplitudes could represent useful neural correlates of the emotional significance and meaning of stimuli.

4.5 Paediatric Disorders and ERP

Bauer and Hesselbrock, (1999) reported P3 amplitude decrements observed at posterior sites among teenagers with conduct disorder problems. However, these were found to normalize in late adolescence, suggesting that the effect was transient, and perhaps related to protracted brain maturation. Auditory P3 topography (specifically ratio of right fronto-central (FC2) to parietal (P4) auditory P300 amplitude) has also been implicated in the prediction of treatment response to stimulants in children diagnosed with attentional deficit hyperactivity disorder (ADHD) (Sangal and Sangal, 2004). It is of note that other pharmacological manipulations have been found to modulate (reduce) the ERP response. For example, effects of anxiolytics have been demonstrated on the N1 and P2 (Abduljawad, Langley, Bradshaw and Szabadi, 2001) and P3 (Semlitsch, Anderer, and Saletu, 1995) components in adults.

In general, the study of ERP component variability in relation to normal affective, cognitive or behavioural traits in children has been quite limited, even though this area of research seems pivotal to efforts to define neurophysiological concomitants of child psychopathology. Of the limited studies available, the evidence shows a modulating effect of anxiety on the NoGo-related N1 component (Baving, Rellum, Laucht, and Schmidt, 2004), on auditory P3 topography (Daruna et al., 1991), and MMN amplitude (Bar-Haim et al., 2003). To the author's knowledge, there are only two studies to have addressed the role of personality traits associated with anxiety on auditory ERP components in children. Both used a standard auditory oddball task (active – Daruna et al, 1991; passive – Bar-Haim et al, 2003), thus

neither may claim to have investigated stimulus novelty in the absence of probability effects.

In the first of these studies, Daruna et al., (1991) investigated P3 amplitude in normally developing young children (three to seven years of age), and reported variability in P3 amplitude topography, which was systematically related to characteristics such as anxiousness as rated by parents using the Conner's Scales. There was no relation to impulsivity also rated using the Conner's. More specifically, this study identified a lateralisation effect with low-anxious children exhibiting smaller P3 amplitudes over the right hemisphere relative to the left, compared with the anxious group who exhibited larger P3 amplitudes over the right relative to the left. This pattern had been previously observed in an earlier study with adults (Daruna and Karrer, 1986). Interestingly, the relationship between P3 asymmetry and anxiety appeared to be relatively specific, as it was not found in relation to an earlier component, namely the N2. More recently, Bar-Haim and colleagues (2003) investigated the mismatch negativity and P1-N1 complex elicited by low probability (deviant) tones in socially withdrawn children. Compared to controls, socially withdrawn children had reduced amplitude of the mismatch negativity, but there was no modulation of the P1-N1 complex.

A modulating effect of anxiety on the N1 component has, however, been demonstrated in another ERP study investigating attentional enhancement to NoGo stimuli (Baving et al., 2004). These authors found that anxious children displayed a significantly larger NoGo-related N1 than did control children, while no group differences were found for the N2 or P3 potentials. They concluded that anxious

children showed early attentional enhancement (N1) to stimuli indicating need for inhibition but not increased resource allocation to actual response inhibition, suggesting that the ability to sustain attention was not impaired in anxiety-disordered children and that these differences in early processing did not impact upon learning. It was however suggested that the lack of N2 and P3 effect could be due to the comparably low processing demands in this paradigm.

Another study published in the same year also used a go/no-go task and indicated that the medial-frontal ERP amplitudes are sensitive to anxiety, and that internalising children show higher amplitudes than controls, especially when anxious (Lewis and Stieben, 2004). These results, which are supportive of Baving et al., (2004), were suggested to reflect individual differences in the effortful regulation of negative emotion.

The N1 enhancement in anxiety-disordered children in the study conducted by Baving et al., (2004) did not appear to reflect generally heightened arousal, as it was specific to the N1 component but not for the other ERP components. These findings suggest that children with anxiety disorders display enhanced attentional orienting to those stimuli that indicate a change in processing demand, but that this is not associated with prolonged modulation of attentional processing (e.g. negative findings in later P3 component).

Summary

The efficient processing of novel events is essential to human behaviour and plays a critical role in adaptation and learning (Daffner et al., 1998; Mesulam, 1998;

Sokolov, 1963), for instance a new sound might be a warning of imminent danger (Barlow, 1988; Friedman et al., 2001). Research has shown that humans vary in the degree to which they actively attend to and explore novel stimuli in the environment (Eaves and Glen, 1996; Lewis and Brooks-Gunn, 1981; McCall, 1994) and links have been identified between low levels of attention to novelty and lower cognitive abilities in children and adolescents (Berg and Sternberg, 1985; Rose et al., 1986). It has also been hypothesised that the influence of attention to novelty may not only be limited to cognitive development but may also influence affective functioning (Eaves et al., 2004).

Current work on temperament has focused on early appearing signs of negative affect and its subsequent link to inhibition and shyness (Prior, 1992) and avoidance of novelty (Kagan et al., 1988a, 1988b). Importantly, studies have also suggested an association between behavioural inhibition and the onset of anxiety disorders in children (Biederman et al., 1993; Rosenbaum et al., 1991a; Rosenbaum et al., 1991b; Schwartz et al., 1999; Van Ameringen et al., 1998). The Behavioural Inhibition System (J.A. Gray, 1982) proposes that anxiety is associated with the processing of novel stimuli and provides a theoretical underpinning to the investigation of novelty appraisal in anxious children.

The investigation of ERP responses to novel environmental sounds may provide empirical evidence for the role of altered brain processing of novelty events in anxious children. Distinct from the standard oddball task, which has been administered in only two studies of personality traits associated with anxiety in childhood, the novelty oddball task may provide a more ecologically valid measure

of brain response to novelty. For instance, a car horn or a dog bark may be more relevant to the BIS model of anxiety than a high or low tone; in other words, it may bear more relevance to the environment and its associated stressors. Furthermore, novel noises are unexpected and may therefore be a better reflection of vigilance and the orienting reflex (as found in the early N1 and N2 ERP waveforms).

Despite the potential importance of efficient novelty processing to cognitive and affective development, and the relationship between novelty and anxiety, no studies have administered the novelty auditory oddball paradigm to children with personality traits associated with anxiety, or to children with diagnosed anxiety disorders. It is considered that this may be an important and highly relevant investigation; one that has the potential to provide empirical support for those models of anxiety (e.g. the BIS) that have proved most influential, and perhaps permit a greater understanding than we currently have of the development and maintenance of childhood anxiety disorders.

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Empirical Paper

Brain response to unexpected novel noises in trait anxious children: ERP evidence for modulation of sensory processing.

The Journal of Cognitive Neuroscience was used as a guide in determining the preparation of this paper.

Abstract

One of the most influential models of anxiety is the Behavioural Inhibition System (J.A. Gray, 1982). This model proposes that anxiety is associated with (over)activation of the "behavioural inhibition system" (BIS); this system may be activated in association with ambiguity and/or novelty. It predicts that activation of the BIS leads to increased vigilance and attention, and greater behavioural inhibition. An important feature is the hypothesised role of novelty in the development and maintenance of anxiety. This relationship was explored by administering a novelty auditory event-related potential paradigm to children aged between 10-14 years with low (n = 12) and high (n = 11) trait anxiety, as determined based on scores obtained from the Spielberger, (1973) State Trait Anxiety Inventory (STAIC). Children in both groups were able to detect the majority of high (target) tones as instructed, and response time was comparable. Novel stimuli (10% probability) elicited a P300 component maximal over midline sites that was significantly larger than that elicited by high target tones (10% probability), and by standard low tones (80% probability). The amplitude and latency of the novelty P3 did not differ between groups. By contrast, the earlier N1 component, which was maximal over the temporal lobes, showed significant group differences in association with novel stimuli. Latency was significantly longer (p = .014), and amplitude significantly higher (p = .004) in the high compared low anxious group. These data suggest subtle processing differences associated with novelty in children with high compared to low trait anxiety, and provide some support for Gray's suggestion that novelty processing is associated with anxiety.

Introduction

Behavioural inhibition in childhood is a personality trait manifesting as avoidance of the unfamiliar, and reflects the tendency to exhibit withdrawal and excessive autonomic arousal to novel situations or events (Rosenbaum, Biederman, and Gersten, 1989). It is identifiable from early childhood, e.g. as early as 21 months (Garcia-Coll, Kagan, and Reznick, 1984; Rothbart, 1988) and has been associated with diagnosis of anxiety disorder (Biederman et al., 1993; Rosenbaum et al., 1991b; Schwartz, Snidman, and Kagan, 1999; review by Fox, Henderson, Marshall, Nichols and Ghera, 2005). Furthermore, evidence from longitudinal studies suggests that inhibitory characteristics remain stable from infancy to pre-school and into adolescence (Aksan and Kochanska, 2004; Schwartz, Snidman, and Kagan, 1999; Schwartz, Wright, Shin, Kagan, and Rauch, 2003). Family studies of behavioural inhibition have also revealed a link between anxious parents and inhibited offspring (Last, Phillips, and Statfeld, 1987) suggesting a genetic or environmentally influenced predisposition. Early childhood research has focused on identifying the behavioural parameters associated with individual variation in behavioural inhibition and children's response to unfamiliar situations or people (e.g., Kagan and Snidman, 1991). This research suggests that a disposition for uncertainty to unfamiliar or novel events and situations can manifest from early childhood, perhaps shaping the development of personality, and in extreme cases leading to an anxiety disorder. In summary, behavioural inhibition may be an early reflection of susceptibility to anxiety.

One important theory exploring the neuropsychology of behavioural inhibition and anxiety is that of Gray (1982; McNaughton and Gray, 2000) who proposed that

anxiety is associated with overactivation of a highly reactive "behavioural inhibition system" (BIS): a system that is activated by stimuli that generate conflict, e.g. new information (novel/unfamiliar events) versus pre-existing schemas. This model proposes that it is this conflict that leads ultimately to behavioural inhibition; increased level of arousal and orientation of attention – preparation for 'fight or flight'.

On a neurological level, Gray, (1982) implicated the septohippocampal system (SHS) and its associated "Papez loop, areas of the temporal and frontal neocortex, as the set of neurological structures which mediate the functions of the BIS. Animal studies appear to support this proposal with lesions of the SHS and related areas producing behavioural effects that Gray interpreted as indicative of reduced anxiety and inhibition. More recent studies have demonstrated right-sided prefrontal activation in behaviourally inhibited children (Kagan and Snidman, 1999) and larger superior temporal gyrus (STG) total and gray and white matter volumes, with a right hemispheric dominance in anxious compared to non-anxious children (De Bellis et al., 2002). Moreover, amygdala hyper-responsiveness to novel faces has been found in adults whose temperament was previously categorised as behaviourally inhibited during infancy (Schwartz et al., 2003). This suggests that those infants who show predispositional traits (e.g. behavioural inhibition) in infancy may be at risk of alterations occurring in the STG and amygdala that represent a vulnerability to developing paediatric anxiety.

From a functional perspective, electroencephalography (EEG) studies have made an important contribution to our understanding of both the development and the

biological underpinning of anxiety disorders, with changes in the brain associated with strange (unexpected) situations being described in infants and children (e.g. Fox, Henderson, Rubin, Calkins, and Schmidt, 2001). In adults, Daffner and colleagues (2000) used EEG to demonstrate the central role of the prefrontal cortex in directing attention to novel events (Daffner et al., 2000), which may suggest that this area is overly active in children who are behaviourally inhibited. The relationship between EEG activity and individual differences in approach and withdrawal behaviours in infancy and childhood has also been extensively explored (Fox et al., 2005, for review). Moreover patterns of frontal lobe EEG asymmetry recorded from infants have been found to predict the later manifestation of a behaviourally inhibited style (e.g. Calkins, Fox and Marshall, 1996).

It is proposed that event-related potentials – ERPs - (which are derived from the EEG trace and more directly time-locked to the occurrence of a novel event) may provide complementary information about novelty-processing in anxious children. Indeed, ERP studies in non-anxious children have suggested that distinct patterns of activity associated with auditory novel stimuli may be detected from early in life (e.g. Määttä, Pääkkonen, Saavalainen, and Partanen, 2005a; Määttä, Saavalainen et al., 2005b). Only two ERP studies have been published in anxious (Daruna, Rau and Strecker, 1991) and behaviourally inhibited (Bar-Haim, Marshall, Fox, Schorr, and Gordon-Salant, 2003) children, and neither examined the effect of stimulus novelty in the absence of stimulus-probability effects.

Novel stimuli have been shown to invoke the orienting response, a shift in attention that enables a rapid response to changes occurring in the environment, such as a

novel sound (Sokolov, 1990). This response is seen as imperative to biological adaptation and survival and has been investigated in recent years in a series of studies in humans using ERPs in the auditory modality (Friedman and Simpson, 1994; Cycowicz and Friedman, 2004; Määttä et al., 2005a, 2005b). One question concerning the processing of novel environmental information is whether it operates at an early stage (e.g. before 200ms) and can influence stimulus encoding. One early-occurring component reliably associated with the orienting of attention towards task relevant stimuli is the N1 (Luck, Heinze, Mangun, and Hillyard, 1990). The N1 has been described as an ERP correlate of very early attentional processing (Hillyard, Hink, Schwent and Picton, 1973; see also Näätänen, 1992 for a review), in particular in relation to novelty (Jääskelälnen et al., 2004). Furthermore the lateral aspect of the N1 is believed to reflect pre-attentive sensory-processing mechanisms in the posterior auditory cortex that occur very early on, indicating the simple detection of a 'different' sound (e.g. see Näätänen, 1992 for review).

The later P300 component has been more frequently associated with novelty in the context of the novelty auditory oddball task, due to the finding that a 'novelty P3' may be distinguished from the usual 'target P3' (Courchesne, Kilman, Galambos and Lincoln, 1984). The novelty P3 is larger over the centro-frontal lobes whereas the target P3 is larger over the centro-parietal lobes. At central midline sites, the novelty P3 appears slightly in advance of the target P3 and is of greater amplitude (see Friedman, Cycowicz, and Gaeta, 2001 for a review). Interestingly, while the target P3 is sensitive to attention to task, the novelty P3 occurs whether or not the individual is attending to task (Courchesne et al., 1984; Friedman et al., 2001). The

novelty P3 has been described as reflecting an orienting response (Friedman et al., 2001), and is associated more with the evaluation of those events for subsequent behavioural action, e.g. flight or fight. This is compatible with the theory of Sokolov (1990), who suggested that novel stimuli evoke the orienting response, which results in a shift in attention that enables an individual to respond quickly to a change in its environment, such as the occurrence of a novel (potentially threatening) noise. Research with both adults and young children has suggested that the frontal lobes are sensitive to the novelty of an event (Daffner et al., 2000, 2003; Knight, 1984; Cycowicz and Friedman, 1997) with novel stimuli being associated with increased P3 amplitude over the frontal lobes compared to standard and deviant stimuli in both adults and children (Friedman and Simpson, 1994; Cycowicz and Friedman, 1997; Daffner et al., 2000, 2003; Määttä et al., 2005b).

It has further been found that with event recurrence the P3 response habituates, leading to a decrease in amplitude (Courchesne, 1978; Friedman and Simpson, 1994). This may explain the lower amplitude of the P3 associated with target and standard stimuli in a novelty oddball task: these stimuli are repeated, while novel stimuli are trial unique. However, it has been shown that the frontal aspect of the novelty P3 may decline with increased exposure albeit to a lesser degree (Cycowicz, Friedman, and Rothstein, 1996; Kazmerski and Friedman, 1995; Knight, 1984), and this may reflect increasing familiarity with this type of stimulus, e.g. in the laboratory the individual forms a category of 'novel stimuli' and classifies incoming novel events into this group. The frontal reduction of the novelty P3 is also consistent with it reflecting an orienting response. Of particular importance to this study is that this evidence and that of previous developmental

ERP findings (Cycowicz et al., 1996) suggests that the brain mechanisms responsible for the processing of novel environmental information are in place at least by the time children are of school age (Cycowicz and Friedman, 1997), and perhaps as early as infancy (Kushnerenko et al., 2002), although there may be increasing efficiency into adulthood.

The N1 and P3 components associated with novelty have been described in children (e.g. Määttä et al., 2005a, 2005b), but converging evidence for the presence of these components may be found in standard oddball paradigms (e.g. low and high tones only), which have been more frequently administered. For example, it has been reported that children have clear signs of selective attention as indicated by enhanced N1 amplitudes to stimuli in the attended channel (attended ear) (Berman and Friedman, 1995; Oades, Dittmann-Balcar, and Zerbin, 1997). Määttä and colleagues, (2005a) reported that in children standard tones presented to either ear elicited a greater N1 when the ear was attended than when it was not. Furthermore in children the N1 latency was significantly longer than in adults. In support of this finding, Määttä et al., (2005b) also investigated the processing of highly novel auditory events in children and adults and reported the N1 component to be more prominent, with longer latencies and larger amplitudes, compared to that elicited by more frequent stimuli.

In the study by Määttä and colleagues (2005a), differences were also described in relation to the P3 component, with the waveforms of adults comprising longer latency novelty P3 components at posterior sites compared to children. This may suggest a difference in processing behaviour between adults and children that

reflect increased brain function related to cognitive stimulus evaluation (e.g. categorising or labelling a stimulus) in the adults. This difference may reflect the fact that the structural maturation of the frontal cortex is not fully developed until late adolescence (Huttenlocher, 1990), and thus stimuli are less well categorised. Moreover, it may also reflect differences between adults and children in their ability to re-orient back to the task following distraction.

The study of variability in ERP components in relation to normal development and functioning in children has been quite limited, even though this area of research seems essential to defining and understanding the neurophysiological aspects of child psychopathology. Current evidence, although limited, shows a modulating effect of anxiety on auditory P3 topography (Daruna and colleagues, (1991); the NoGo-related N1 component (Baving, Rellum, Laucht, and Schmidt, 2004), and MMN amplitude (Bar-Haim et al., 2003). Only the studies by Daruna et al., (1991) and Bar-Haim et al., (2003) addressed the role of personality traits associated with anxiety on auditory ERP components in children, however both used a standard auditory oddball (i.e. no novel stimuli) hence therefore have not investigated the novelty of the stimulus without the effects of stimulus probability.

Of particular interest to this study is Baving and colleagues, (Baving et al., 2004) investigations into attentional enhancement to NoGo stimuli in anxious children. They reported that anxious children displayed a significantly larger NoGo-related N1 than did control children and concluded that anxious children showed early attentional enhancement (N1) to stimuli, indicating need for inhibition. However the ability to sustain attention was not impaired in anxiety-disordered children and

the reported differences in early processing did not impact upon learning, hence no group differences were found for the later P3 component. Although the P3 elicited in Baving's study cannot be described as a correlate of novelty processing, i.e. not the novelty-P3, it is of relevance that there was evidence of a dissociation in the effects of anxiety on ERP components.

Studies investigating the influence of anxiety and anxiety-related disorders on ERPs have frequently reported differences in ERP components between anxious and non-anxious adults. For example, N1 and N2 amplitudes for both target and non-target tones were found to be significantly larger in individuals with panic disorder (Iwanami, Isono, Okajima, and Kamijima, 1997; Knott, Lapierre, Fraser, and Johnson, 1991), increased P3 latencies were described in subjects with social phobia, (Sachs et al., 2004) and significantly longer inter-peak latencies were reported in adults with generalised anxiety disorder (GAD) (Drake, Pakalnis, Phillips, Padamaden, and Hietter, 1991).

Studies investigating the influence of paediatric disorders on ERP components are by comparison limited and although relevant, are not always specific to anxiety. Bauer and Hesselbrock, (1999) reported reduced P3 amplitude at posterior sites among teenagers with conduct disorder problems. Furthermore, auditory P3 topography has been investigated in children with attentional deficit hyperactivity disorder (ADHD) as it was found that this component was implicated in the prediction of response to treatment in this subject group (Sangal and Sangal, 2004), it has also been shown to be atypical in normally developing anxious children (Daruna et al., 1991). This latter study in particular identified a lateralisation effect

with low-anxious children exhibiting smaller P3 amplitudes over the right hemisphere relative to the left, compared with the anxious group who exhibited larger P3 amplitudes over the right relative to the left hemisphere. This pattern had been previously observed in an earlier study with adults (Daruna and Karrer, 1986), moreover the observed relationship between P3 asymmetry and anxiety appeared to be relatively specific, as it was not found in relation to the earlier N2 component. In a more recent study, the mismatch negativity and P1-N1 complex elicited by low probability (deviant) tones was investigated in socially withdrawn children (Bar-Haim et al., 2003). These authors found that in comparison to controls, there was reduced amplitude of the mismatch negativity in the withdrawn children, but no group differences for the P1-N1 complex. According to Gomes and colleagues (Gomes et al., 2001) N1 topography in both adults and children indicates the existence of a central and lateral component, the latter of which is maximal at temporal lobe sites (e.g. T3, T4). The study by Bar-Haim and colleagues (2003) investigated the central component but not the lateral component, so cannot claim to confirm that N1 effects were absent. A study in the following year using a go/no-go task indicated that the medial-frontal ERP amplitudes (including the central N1) are sensitive to anxiety, and that internalising children show higher amplitudes than controls, especially when anxious (Lewis and Stieben, 2004). However, as with the study by Baving and colleagues, (2004), the focus of this study was not on stimulus novelty.

Efficient novelty processing is potentially important to both cognitive and affective aspects of child development, hence the relationship between novelty and anxiety may be of significance. Yet despite this awareness, there is currently little research

linking these subject matters and no studies have administered the novelty auditory oddball paradigm to children with personality traits associated with anxiety, or to children with diagnosed anxiety disorders. It is therefore considered that a greater understanding into the development and maintenance of childhood anxiety disorders may be found through providing empirical support for those models of anxiety (e.g. the BIS) that have proved particularly influential. Gray (1982, Gray and McNaughton, 2000) hypothesised that anxious children respond differently to novel events. It would therefore be prudent to test this theory by administering a novelty oddball paradigm.

Research has demonstrated that the components associated with novelty appraisal (i.e. N1 and novelty P3) are typically elicited in novelty oddball paradigms, where deviant (e.g. high 'target' tones – low probability) and novel stimuli (e.g. novel noises – also low probability) are infrequently interspersed with standard stimuli (e.g. low tones – high probability). Distinct from the standard oddball task, which has been administered in only two studies of personality traits associated with anxiety in childhood, the novelty oddball task may provide a more ecologically valid measure of brain response to novelty. For instance, a car horn or a dog bark may be more relevant to the BIS model of anxiety than a high or low tone; in other words, it may bear more relevance to the environment and its associated stressors. Furthermore, novel noises are unexpected and may therefore be a better reflection of vigilance and the orienting reflex (as found in the early N1 waveform).

Hypotheses

The aim of this study was to investigate ERP responses to novelty in high and low anxious children using a novelty auditory oddball event-related potential (ERP)

paradigm. As clinically anxious children often show fear of novelty (Daruna et al., 1991) it was hypothesised that ERP components associated with novel stimuli would produce group differences between those children with high compared to low trait anxiety.

1. It is hypothesised that the P3 response to novel stimuli will be of greater magnitude than the P3 response to both types of familiar tones (Standard/Low tones and Deviant/Target/High tones), and that this pattern of activity will be present for both the high and low trait anxious groups.

2. In accordance with the adult literature, it is hypothesised that those children with high compared to low trait anxiety will show significantly increased N1 and P3 amplitude in response to novel stimuli.

Methods

Permission for this study was granted by the Ethics Committee of the School of Psychology, University of Southampton, UK - (see Appendix 3).

Recruitment:

The initial research proposal outlined a recruitment plan that involved contacting local primary and secondary schools to discuss the study in detail with Head Teachers and their staff. Following this, the children were to be issued with a comprehensive information letter and consent form to take home to their parents. All schools who had previously consented to take part in research conducted at the University and who were therefore already on the School of Psychology

Department's database were contacted. Unfortunately, all Head Teachers contacted declined to allow the information to be given to their pupils. Schools that were not on the database were also contacted, but similarly declined to take part. The most frequent reason given by Head Teachers for this decision was that they were concerned that parent's would react negatively to the ERP technique. Although attempts were made to alleviate this concern, e.g. offering to visit schools to discuss the study in more detail, meeting with parents and providing additional written information, the Head Teacher's remained unwilling to participate. With the consent of the School of Psychology Ethics Committee, a recruitment poster, requesting participants for the study was designed and displayed in prominent places throughout the University campus. Departmental staff were also approached and asked if their children would consider taking part in the study. All children who took part in the study were recruited via University employees or through the poster advertisement.

Participants:

Twenty-three typically developing children consented to be recruited into the study (aged 10-14 years, *M* age 12y 2mo, 12 boys). All participants were issued with an ID number to ensure confidentiality when data were stored and analysed. All children attended mainstream schools, and none had a history of head trauma, neurological or psychiatric disorder, learning disability, and/or hyperactivity (confirmed by a checklist completed by parents - Appendix 4). Those parents of children interested in participating in the study telephoned the researcher, and were sent an information sheet detailing the nature of the study and what would be required from the children (Appendix 5). Informed written consent to participate in the study was obtained from the children and their parents (Appendices 6 a, b). A

mutually convenient time was arranged for the children to come to the ERP laboratory in the School of Psychology at Southampton University. This was typically after school or on a Saturday. Hearing was not formally assessed for this study, but parents did not report any abnormality; children were not assessed if they had a cold or had a hearing deficit that was sufficient to result in use of a hearing aid. All children attended for one session which lasted approximately one hour. They received a small honorarium of £5 for their participation.

Anxiety Measure:

The State-Trait Anxiety Inventory for Children (STAIC; Spielberger, 1973) was used in this study to determine variation in trait anxiety, and to parse groups for ERP analysis (Appendix 7). The STAIC is a self-report measure consisting of 20 statements (maximum score = 60) designed to assess state and trait anxiety in children. The A-State scale measures transitory anxiety states: subjective, consciously perceived feelings of apprehension, tension and worry that vary in intensity and fluctuate over time. The A-Trait scale measures relatively stable individual differences in anxiety susceptibility: differences between children in the tendency to experience anxiety states. High A-Trait children are more prone to respond to situations perceived as threatening (with elevations in A-State intensity) than low A-Trait children.

According to Spielberger and colleagues (Spielberger, Gorsuch, and Lushene, 1970) the internal consistency of the STAIC scales is good and the test re-test reliability of the A-Trait scale is moderate (.65 for males and .71 for females). The test-re-test correlations for the STAIC A-State scale are comparably low (.31 for males and .47

for females), however it is argued that this finding is anticipated given that it is a measure designed to be sensitive to the influence of situational factors (Spielberger et al., 1970). A more recent study has examined the reliability and validity of three traditional and three new childhood anxiety questionnaires (Muris, Merckelbach, Ollendick, King, and Bogie, 2002). Their results concluded that anxiety questionnaire scores correlated substantially with each other, with strong associations in particular found between the total STAIC and Revised Children's Manifest Anxiety Scale (RCMAS) scores ($r = 0.88$). The authors concluded that the results found demonstrated good internal consistency between childhood anxiety scales generally. A subsequent study evaluated the ability of the RCMAS, the STAIC and the Child Behaviour Checklist (CBCL) to discriminate between children and adolescents with anxiety disorders and those without, those with anxiety disorders and those with externalising disorders, and treatment response (Seligman, Ollendick, Langley, and Baldacci, 2004). The authors reported considerable support for these measures in their capacity to discriminate between conditions, although they remarked on a need for improvement in regards to diagnostic overlap between anxiety instruments and instruments for other affective disorders such as depression.

Novelty Auditory Oddball:

ERP data were elicited by an 'Auditory Novelty Oddball Paradigm' (developed by Dr Torsten Baldeweg, Reader in Developmental Cognitive Neuroscience, Institute of Child Health, UCL, and recently published: C. H. Salmond, F. Vargha-Khadem, D.G. Gadian, M de Haan, and T. Baldeweg, 2006 (in press). This consisted of a series of tones and novel sounds presented in one 10 minute session: Standard tone

(1kHz, 5ms rise and fall time, 75 dB sound pressure level, 80% probability); deviant high – target - tones (1.5kHz, 10% probability); computer-generated novel environmental sounds, e.g. dog bark, car horn, whistle, (10% probability). Stimulus-onset-asynchrony (SOA) was 900ms and each tone/novel sound was of 200ms duration.

Procedure:

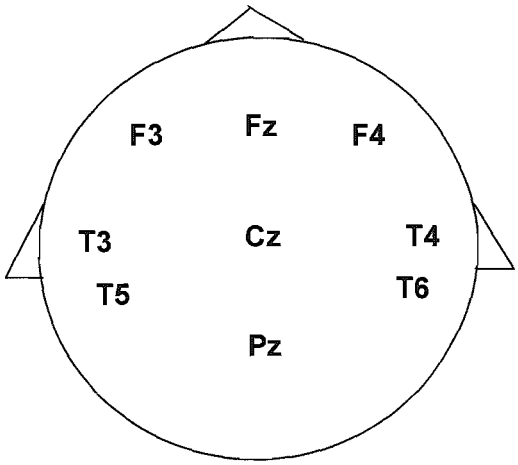
The children were invited into the ERP Laboratory and the various equipment items were shown and explained. They were advised that parents could remain in the room with them during the EEG recording but preferably not during completion of the STAIC as this could have an effect on the reliability of their scores (particularly if parents were observing their answers). The children, and parents present, were encouraged to ask any questions or raise any concerns and to inform us immediately if they felt at all uncomfortable or wished to stop the assessment. The aim was to ensure that all children felt as relaxed and comfortable as possible throughout the assessment. The STAIC took approximately 10 minutes to complete and no concerns were raised. The STAIC-trait was administered first, followed by the STAIC-state scale. The ERP recording was performed immediately after children had finished filling in these scales.

EEG recording:

Three measurements of the child's head were recorded: circumference; between the eyebrows to the back of the head (along the midline); and, from ear to ear. These measurements enabled the positioning of electrodes on the scalp at similar positions in all children, accounting for individual variability in head size, e.g. the Cz

electrode was positioned at the top of the head exactly halfway between the eyebrows and the bump at the back of the head, and exactly halfway between the ears. The remaining electrodes were sited according to calculations based on the conventional 10-20 system of lead placement (Jasper, 1958). This model involves placing leads at either 10% or 20% distance from each other according to the child's head size. Three leads were positioned along the midline: anterior to posterior (Fz- over the frontal lobes. Cz – the vertex over the posterior frontal lobes, Pz – over the parietal lobes: see Figure 1). Additional leads were placed over the left (F3, T3, T5) and right (F4, T4, T6) hemispheres (see Figure 1). All leads were held in place with a 'vasaline' like conductive gel. Leads were placed above and below the right eye (to indicate when the child blinked). Blinks are very large compared to an ERP component, and can be detected in scalp leads as well as the eye leads. It is possible to extract blinks from the EEG trace using an automatic procedure based on a study by Semlitsch and colleagues (Semlitsch, Anderer, Schuster, and Presslich, 1986). Three other leads were placed: a lead on the forehead over the left eyebrow served as the ground lead, and two leads placed on the bone behind each ear (mastoid) served as the reference electrodes. Impedance values reflect the quality of the recording and in line with convention were kept below 5kΩ. EEG data were amplified using a Neuroscan NuAmps system and digitised at a rate of 500Hz (band-pass 0.05-70Hz).

Figure 1. Montage showing position of the leads used in this study during EEG recording (F = Frontal; F3, Fz, F4), T = Temporal (left hemisphere: T3, T5 and right hemisphere: T4, T6), C = Central (Cz) and P = Parietal (Pz).



ERP Stimulus Presentation

The children were seated facing a computer screen. Stimuli were presented through speakers, and during the task pictures of animals and children's television characters appeared on the screen in order that they had something to look at. The pictures changed at a rate of every 45 seconds, but not at the same time as the presentation of a novel stimulus. Children were asked to press a mouse button when they heard a high (target) tone, but they were not informed about novel stimuli. Responses to the target tone were monitored on-line to ensure that the children sustained attention for the duration of the task. The entire assessment took approximately 45 minutes to complete and no concerns were raised. The ERP procedure took approximately 20 minutes, with 10 minutes actual recording time (with a short break midway) depending on the child's level of co-operation. Between 550 and 750 events were obtained from each child.

The 'state' part of the STAIC was re-administered after the ERP paradigm in order to assess post-task levels of anxiety. The children were also asked to describe any sounds from the ERP task that they particularly remembered, e.g. a dark bark may have been particularly salient to some children, but most children simply recalled all of the different types of noises, e.g. dog bark, horn, drum, etc., so these reports were not analysed further. All children and their parents were given a verbal debrief explaining the study in more detail and thanked for their time and participation.

ERP Processing:

ERP components were extracted from the EEG trace and processed offline. Every time a stimulus occurred a code appeared at the bottom of the EEG. There was a different code for low tones, high-target tones and novel noises. Once blinks and muscle artefact had been removed the EEG was divided into chunks centred on the stimulus codes (-200 to 1000ms: 0 = the stimulus code). These EEG epochs were then aligned across all sites (baseline corrected: -200 to 0ms), and any epochs contaminated by persisting muscle or movement artefact (+/- 75μV) removed by an automatic process, and also by manually inspecting all epochs. The remaining epochs were then averaged together according to stimulus type (Standard Low Tones; High-target Tones; Novel Stimuli). ERP averages obtained from individual children were averaged again into groups ('Grand Averages': Low Anxious Group and High Anxious Group).

The percentage of total trials rejected due to movement artifact was comparable between groups (Low Anxious: M = 5.9%, SD = 4.7, High Anxious: M = 8.8%, SD

= 6.6; $t(21) = -1.25$, $p = .225$). Similarly, the mean number of trials included in the grand averages for each stimulus type did not significantly differ between groups (Standard Tones: Low Anxious – $M = 520$, $SD = 80$, High Anxious – $M = 481$, $SD = 71$, $t(21) = 1.22$, $p = .233$; High-target Tones: Low Anxious – $M = 62$, $SD = 8$, High Anxious – $M = 56$, $SD = 8$, $t(21) = 1.62$, $p = .119$; Novel Noises: Low Anxious – $M = 60$, $SD = 10$, High Anxious – $M = 55$, $SD = 8$, $t(21) = 1.35$, $p = .191$).

The peak amplitude and latency of both the N1 component and the subsequent positive P3 component were measured where these components appeared maximal, and where group differences were observed (by comparing the grand average waveforms). The N1 component consists of central and lateral subcomponents (Gomes et al., 2001), with the latter maximal over the temporal lobes (Woods, 1995), and of particular prominence in children (Bruneau, Dourneau, Garreau, Pourcelot, and Lelord, 1997; Tonnquist-Uhlen, Ponton, Eggermont, Kwong, and Don, 2003). The lateral N1 (henceforward: N1) was measured at temporal lobe sites (T3, T4) between 70-190ms. The P3 was evident at all midline sites, so was measured at 250-450ms at Fz, Cz, and Pz. Amplitudes and latencies were measured manually. These values were entered into an SPSS database.

Statistical Analysis:

Behavioural data were compared between groups using T-tests; data were explored (Kolmogorov-Smirnov test) and found to be compatible with parametric assessment. Group effects were then tested separately for the amplitude and latency of the N1 and P3 components, using four mixed-factorial ANOVA models (1. N1

latency; 2. N1 amplitude; 3. P3 latency; 4. P3 amplitude). For N1 amplitude and latency there were two within-group factors (1. stimulus: standard, high-target, novel; 2. side: T3, T4), and one between-group factor (group: low vs. high trait anxious). For the P3 component there were two within-group factors (1. stimulus: standard, deviant, novel; 2. site: Fz, Cz, Pz) and one between-group factor (group: low vs. high trait anxious). In each case age was entered as a covariate as the amplitude and latency of these components are reportedly sensitive to age (e.g. Gomes et al, 2001). T-tests and correlation analyses (across groups and one-tailed) were conducted to explore significant group differences. For all tests the significance threshold was set at 0.05.

Results

STAIC-trait anxiety scores ranged from 23 to 50. In order to compare ERP data a median split was made at a score of 33. This resulted in a 'Low Trait Anxious' and a 'High Trait Anxious' group. The composition and mean scores for the trait and state anxiety (before and after ERP) for each group, are provided in Table 1. Groups did not significantly differ in terms of age, gender, or STAIC-state (pre or post) scores. Furthermore, there was no significant correlation between trait and state anxiety (pre-ERP state scores: $r = .154$, $p = .241$; post-ERP state scores: $r = .154$, $p = .241$); an unusual finding probably due to the more limited distribution of state anxiety scores (see Table 1).

Table 1: Age (standard deviation) and gender composition of the Low and High Trait Anxious groups, and the mean scores (standard deviations, and ranges) for the trait and state anxiety measures.

	Low Trait Anxious n = 12	High Trait Anxious n = 11
Age	12y 2mo [1y 7mo]	12y 2mo [1y 11mo]
Gender	5 boys	7 boys
Trait Scores	29.8 [2.7] (23-33)	40.1 [4.0] (36-50)
State Scores pre ERP	29.6 [3.1] (24-34)	30.5 [2..2] (27-34)
State Scores post ERP	29.2 [2.7] (24-34)	29.5 [2.9] (27-34)

Behaviour:

As indicated in Table 2, the groups did not differ on any behavioural measure associated with the ERP task (all $p > .1$). All children sometimes made an incorrect response to novel stimuli. The lack of group differences suggests that all children understood the task instructions.

Table 2. Mean (standard deviation) hit-rate and response times to the high-target tones, and rate of accidental responses to novel stimuli in the low and high trait anxious groups.

	Low Trait Anxious	High Trait Anxious
Hit Rate (%)	85.8 [13.6]	84.6 [14.1]
Response Time (ms)	205.0 [17.1]	218.3 [23.8]
Incorrect Response to Novel Stimuli (%)	13.5 [13.7]	10.1 [15.1]

ERP Components:

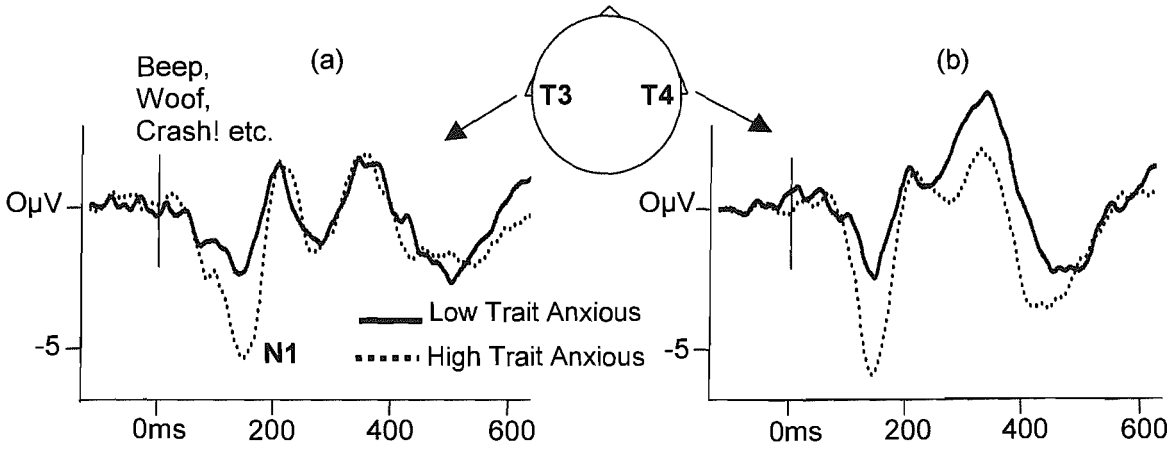
The N1 component was examined first. The mean amplitudes and latencies for the N1 component at T3 and T4 are presented in Table 3. There was a significant group by stimulus interaction for N1 latency [$F(2, 40) = 6.84$, $p = 0.003$], and N1 amplitude [$F(2, 40) = 3.28$, $p = 0.048$], but no other main effects of stimulus or group, and no effect of age (all $p > .1$). In summary, N1 latency associated with novel stimuli was delayed in high trait anxious children compared to standard stimuli, whereas for low anxious children it was the opposite. Novel-N1 amplitude was highest in high anxious children, whereas high-target N1 amplitude was highest in low anxious children. As revealed in Table 3, significant group differences were only found in relation to novel stimuli. Figure 2 shows that the amplitude of this N1-novel component was indeed larger in high compared to low trait anxious children.

Table 3. Mean amplitude and latency for the N1 component at temporal lobe sites for all stimuli.

			Low Trait Anxious	High Trait Anxious
T3	Standard	Amplitude (μV)	-1.8 [1.3]	-3.2 [2.2]
		Latency (ms)	153.2 [14.9]	133.1 [34.3]
	Target	Amplitude	-4.6 [2.0]	-4.8 [3.2]
		Latency	147.5 [18.9]	147.3 [21.2]
	Novel	Amplitude**	-3.3 [2.1]	-6.1 [2.2]
		Latency*	128.3 [23.1]	147.1 [14.9]
T4	Standard	Amplitude	-2.2 [1.3]	-2.4 [2.4]
		Latency	158.0 [19.9]	140.7 [29.8]
	Target	Amplitude	-4.7 [2.9]	-5.8 [5.9]
		Latency	151.0 [21.5]	145.1 [21.3]
	Novel	Amplitude*	-3.2 [2.9]	-6.4 [3.8]
		Latency	134.3 [23.6]	146.2 [16.1]

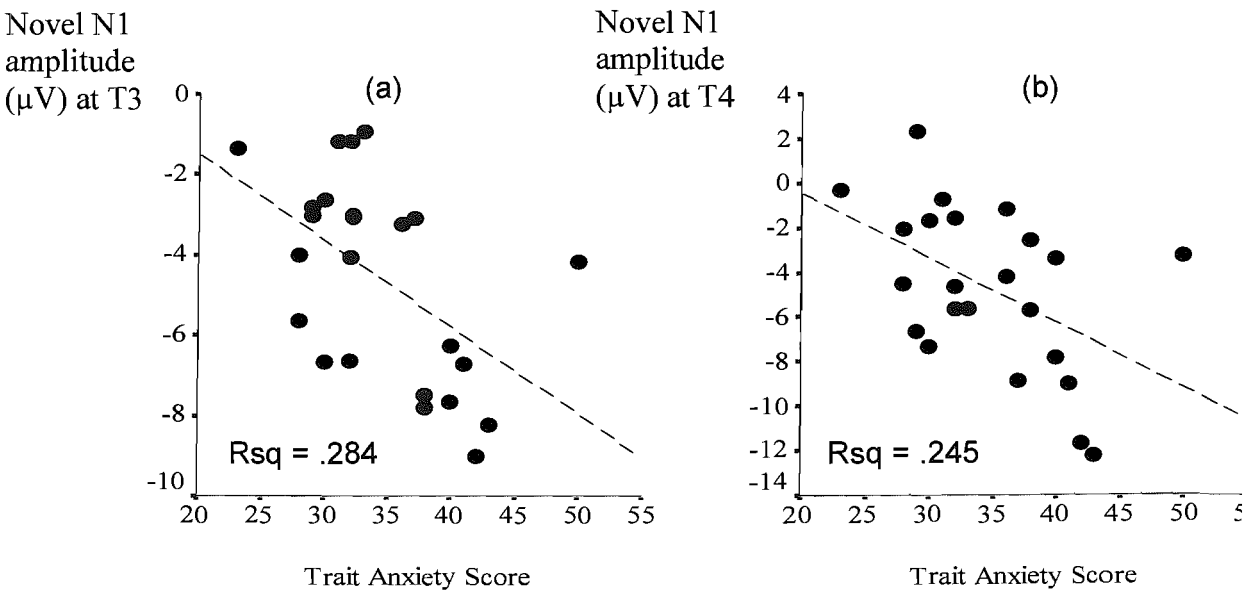
* $p < .05$, ** $p < .01$

Figure 2: Novelty-N1 waveforms over the left (a) and right (b) temporal lobes.



While there were no significant correlations between trait score and N1 latency at T3 (r = .338, p = .115), or T4 (r = .239, p = .272), significant associations were found for N1 amplitude. As revealed in Figure 3, N1 amplitude increased with increasing trait anxiety score at both T3 (r = -.533, p = .009) and T4 (r = -.496, p = .016).

Figure 3: Novelty-N1 amplitude over the left (a) and right (b) temporal lobes and trait anxiety scores.

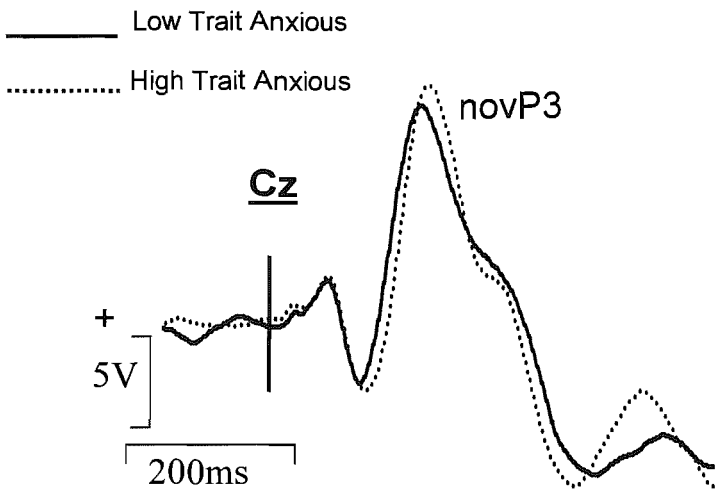


Novel stimuli are often associated with increased P3 amplitude, which is maximal in adults over the centro-frontal lobes, compared with standard or deviant stimuli (Friedman and Simpson, 1994; Cycowicz and Friedman, 1997; Daffner et al, 2000). In line with this, a P3 component, evident at approximately 300ms at all midline sites was found (see Figure 4, for Cz) and appeared largest for novel stimuli (see Table 3). However, controlling for age there were no significant group differences for amplitude or latency, or any other significant main effects or interactions, suggesting that this component was not significantly influenced by anxiety.

Table 4. Mean amplitude and latency for the P3 component at midline sites.

			Low Trait Anxious	High Trait Anxious
Fz	Standard	Amplitude (μV)	-1.1 [1.5]	-2.1 [2.4]
		Latency (ms)	327.5 [27.3]	333.8 [32.7]
	Target	Amplitude	0.6 [5.8]	-0.9 [5.6]
		Latency	311.2 [25.6]	328.0 [24.4]
	Novel	Amplitude	5.4 [4.8]	5.2 [4.0]
		Latency	314.3 [33.3]	315.8 [31.5]
Cz	Standard	Amplitude	-1.6 [2.1]	-3.1 [1.6]
		Latency	330.0 [28.2]	339.1 [31.7]
	Target	Amplitude	3.5 [6.1]	1.4 [6.7]
		Latency	306.7 [33.8]	327.6 [31.4]
	Novel	Amplitude	5.8 [3.8]	5.1 [6.7]
		Latency	307.5 [32.0]	324.9 [33.2]
Pz	Standard	Amplitude	-0.1 [1.0]	-2.6 [1.5]
		Latency	332.8 [34.7]	321.5 [43.9]
	Target	Amplitude	7.7 [3.4]	5.4 [4.7]
		Latency	308.8 [25.1]	328.7 [23.9]
	Novel	Amplitude	6.9 [4.6]	6.4 [5.1]
		Latency	319.2 [11.9]	316.4 [21.5]

Figure 4: Novelty P3 component at site CZ for low and high trait anxious groups.



In summary these results suggested that there was subtle ERP evidence of sensitivity to novel stimuli in the high anxious group. However no behavioural differences between the groups were found, suggesting that both groups understood the task instructions and that anxiety did not influence performance.

Discussion

There is currently a limited literature investigating the role of trait anxiety on cognitive, affective and behavioural processes in children. Of the two studies that have provided evidence for a moderating role of anxiety in this subject group, neither controlled for stimulus probability (i.e. Bar-Haim et al, 2003; Daruna et al., 1991). The present study has extended the literature through the use of the novelty auditory oddball paradigm which controls for stimulus probability allowing a demonstration of anxiety-modulation of the ERP waveform associated with novel stimuli.

These data are compatible with Gray's (1982) theory of a BIS, which suggests that novel stimuli generate conflict, leading to heightened arousal and vigilance. The increased N1 latency and amplitude reported here suggests that it is the very early (within 200ms) stages of sensory-processing that are influenced by variations in trait anxiety. This is further demonstrated by the comparable P3 response found between the high and low anxious children. The subsequent P3 response is believed to reflect an evaluative stage of novelty processing e.g. "what was that?" (Friedman et al., 2001) and this lack of difference between the two groups indicates that in typically developing children, the effects of anxiety on novelty processing is subtle, i.e. it is confined to very early stages of processing and does not impact on more conscious appraisal of the event, moreover, it is not sufficient to detract children's attention away from the task-at-hand (evident in the comparable hit rates). This may not of course be the case for children with a clinical diagnosis of anxiety and it would be interesting to investigate the extent to which both the N1 and P3 components are different in this subject group.

The differences found in early sensory processing between the high and low trait anxious groups may suggest that anxious children are hypersensitive to the novelty of an event. Support for this suggestion may be found from the theories of Eysenck (1992) and Gray (BIS: 1982) who proposed that anxious individuals are sensitive to events or situations that are mildly threatening or ambiguous/novel. Evidence from adult and child studies appears to support this suggestion with anxious individuals exhibiting enhanced subjective and physiological responses to mildly threatening stimuli or situations (Barlow 2002; Birbaumer et al., 1998; Lang, Bradley, Cuthbert, 1998; Pine et al., 2000), suggesting that they may differ from non-anxious

individuals in their level of learned-sensitivity to such stimuli. Moreover, although behaviourally inhibited children avoid unfamiliar situations or events, they reportedly remain aware and vigilant of their surroundings (Kagan, Reznick, Snidman, Gibbons, and Johnson, 1988). According to Gray's (1982) theory of an (over)active BIS, the occurrence of a novel event interrupts behaviour (i.e. inhibition of current behaviour to process the new stimuli), if necessary allowing future behaviour to be executed more slowly and carefully (hyperarousal and vigilance). In theory, this could account for the increased amplitude and longer latencies recorded in the high anxious group of children, although the early timing of this response denotes that it is probably pre-conscious and independent of awareness, and more relevant, the P3 response did not differ between groups. It is also unclear as to the extent to which N1 modulation reflects a stable sensory-processing bias. State-anxiety was low in the present study, perhaps partly due to the extra care taken to make the children feel at ease in the ERP laboratory (e.g. playing music while the leads were placed). The children were given plenty of time to acclimatise and ask questions before they were asked to complete questionnaires and participate in the ERP experiments. Future work should examine the possibility that state anxiety may contribute to ERP changes.

There is evidence that children with high trait anxiety have deficits in cognitive processing (e.g. Hadwin, Frost, French, and Richards, 1997; Hadwin et al., 2003; Hadwin, Garner, Perez-Olivas, 2006; for a review Vasa and Pine 2004), particularly in the domain of working memory (Terry and Burns, 2001). The novelty auditory oddball task is simplistic but nevertheless requires a degree of sustained attention. The extent to which working memory was recruited is not clear, but it is important

to point out that low and high trait anxious children performed similarly, which suggests that both groups understood the task instructions and that anxiety did not exert an influential role on overall performance. Interestingly, both groups of children sometimes responded incorrectly to novel stimuli, suggesting that the ambiguity of the stimulus had an effect on both groups of children irrespective of level of anxiety. However, the increased N1 latency and amplitude in the high trait anxious group compared with the low trait anxious children suggests that there is an influence of anxiety in this group at the initial stages of sensory-processing, albeit subtle.

Early studies exploring the N1 component in adults with brain lesions reported reduced auditory N1 amplitude in patients with lesions to the temporal lobe (Knight, Hillyard, Woods and Neville, 1980, 1981; Knight, Scabini, Woods and Clayworth, 1988). Other investigators have provided evidence (e.g. using ERP component source localization techniques) to also suggest that the auditory N1 component is generated in the auditory cortex of the temporal lobe (Jääskelälnen et al., 2004; Näätänen and Picton, 1987; Woods, 1995). Converging evidence comes from experimental conditioning studies which hypothesise that amygdala activity is modulated by inputs from the superior temporal gyrus (STG), which in turn is connected to other structures involved in higher cognitive processing of the fear experience (Quirk, Armony, and LeDoux, 1997). In support, functional magnetic resonance imaging studies (fMRI) have revealed increased amygdala activation to be associated with fearful faces in children (Baird et al., 1999). Furthermore, quantitative MRI studies have reported significantly larger STG volumes, with a right hemispheric dominance (De Bellis et al., 2002; Milham et al., 2005) and

increased amygdala volumes (De Bellis et al., 2000), in clinically anxious children. These findings are compatible with earlier suggestions linking increased reactivity of the amygdala to the development and maintenance of an inhibited temperament (Kagan, Reznick, Clarke, Snidman, and Garcia-Coll, 1984; Kagan et al., 1988a). Prefrontal activation has also been associated with anxiety. Several studies have demonstrated right-sided prefrontal activation in behaviourally inhibited children (Kagan and Snidman, 1999) who tend to be avoidant of situations that are novel (Kagan, Reznick and Snidman, 1987; Schwartz, 2003) and who are often predisposed to develop childhood anxiety disorders (Biederman et al., 1993). The results of the present study are consistent with the finding that there are subtle structural differences in the temporal lobe in children who are anxious, but further study is required to replicate this finding, and further, to investigate any relationship with frontal lobe abnormality.

Several EEG studies have suggested that hemispheric asymmetry may be influenced by anxiety. Heller, (1997) reported larger asymmetry in favour of the left hemisphere in anxious participants with self-reported anxious apprehension, but right parietal activity during anxious arousal. Similarly Davidson and colleagues (Davidson, Abercrombie, Nitschke, and Putnam, 1999) reported greater electrical activity in the right hemisphere in individuals with a high anxious arousal. A positron emission tomography (PET) study also revealed healthy subjects with high trait anxiety to have greater right-left ratios of central metabolism than low trait anxiety subjects (Stapleton et al., 1997). In their quantitative MRI study, De Bellis, (2002) proposed that anxious children without a history of trauma have a propensity for larger right amygdala and STG volumes than non-anxious children, resulting in

the development of those personality traits (behavioural inhibition) associated with developing an anxiety disorder. In other words, children predisposed to having abnormal right temporal lobe structures are more likely to be anxious. While Daruna et al (1991) reported some asymmetry in the laterality of the P3 component associated with low and high anxiety, she did not find a difference for earlier components (e.g. the N2). In the present study there were no laterality effects – the N1 recorded from the left and right temporal lobe was consistently larger in high compared to low trait anxious children.

While anxiety disorders may result from subtle abnormality in brain structure and function, it is also feasible that the brain may be shaped by chronic anxiety. In other words, the abnormal structure and function result from chronic anxiety. Longitudinal studies such as that of Schwartz and colleagues (2003) found amygdala and STG abnormalities (hyperresponsiveness) to novel faces in adults whose temperament was previously categorised as behaviourally inhibited during very early childhood. It may therefore be the case that those infants who show predispositional personality traits are at risk of maladaptive brain plasticity, particularly in those areas associated with anxiety, (i.e. STG and amygdala) and that this may increase the likelihood of anxiety disorder in later childhood. It has already been documented that children who are behaviourally inhibited are more likely to develop a clinically significant anxiety disorder in later life (Biederman et al., 1993; Rosenbaum, Biederman, Hirshfeld, Bolduc, and Chaloff, 1991a; Rosenbaum et al., 1991b; Schwartz et al., 1999; Van Ameringen, Mancini, and Oakman, 1998).

There are limitations to the study which need to be acknowledged, and suggestions for further research. First, recruitment difficulties meant that the research sample was relatively small. A larger sample may have provided more statistical power to the study, as some of the results fell just short of significance (e.g. T3 novelty latency correlating with trait anxiety scores; $p = .057$). Second, although the effects were maximal over the temporal lobes, it is not possible to confirm that the 'abnormal' generator of the N1 was located in the temporal lobes – this may only be inferred. Thus any relationship between the anatomical studies described above and the functional group differences described in the present study, and indeed with the BIS model, is implied rather than confirmed. Thirdly, no other measures of personality were administered but it is of interest to consider whether other traits (e.g. introversion / extroversion – see Cahill and Polich, 1992; Daruna, Karer, and Rosen, 1985) modify these ERP components. However, there is some evidence for selectivity in that Daruna et al (1991) also investigated impulsivity but did not find the same P3-topographic effects as were found for anxiety. Fourthly, it is of interest to consider the extent to which the N1 variation is associated with performance on neuropsychological measures of attention, and perhaps working memory, in order to confirm that any hypervigilence does not interrupt the learning process. Finally, the paradigm used only focused on auditory processing, and it is therefore difficult to generalise these findings to other modalities. Replications of this research involving for instance sight, touch and even taste would be both useful and interesting in demonstrating the applicability of the findings to other sensory modalities. Moreover, the use of techniques such as fMRI in conjunction with ERP techniques may provide a complimentary perspective linking the functional with the structural findings of this study. Most importantly, however, given that a

significantly increased N1 component latency and amplitude was found in a normal population of children with increased anxiety, it would be of interest to examine this ERP component in children with clinically diagnosed anxiety disorders.

Although the interpretation of these findings must remain preliminary, this study is significant because to the author's knowledge it is the first ERP study to investigate the appraisal of novel auditory stimuli in children with normal variations of anxiety. Moreover, this study has confirmed that in a normal child population, early sensory processing (N1) of novel stimuli is affected by anxiety.

Clinical Implications

These results make an important contribution to the neuroscience literature, but they also have potential clinical implications. The characterisation of anxiety-associated changes in the processing of novel information in healthy children may help to identify neurobiological abnormalities associated with behavioural pathology. This study examined the role of psychobiology in paediatric anxiety and has confirmed an important tenet of the BIS model that novel events are processed differently in normally developing children with high compared to low levels of anxiety. Avoidance or withdrawal from novelty can be indicative of a behaviourally inhibited temperament, which has been consistently identified as an important premorbid factor in many psychiatric disorders, specifically anxiety (Biederman et al., 1993; Rosenbaum et al., 1991b; Schwartz et al., 1999; review by Fox et al., 2005). Such behaviour, if present chronically may have the potential to modify brain plasticity and perhaps lead to clinical disorder in later life. It is of particular interest that pharmacological studies have already demonstrated in adults that the

N1 may be normalised by administration of anti-anxiolytic medications (Abduljawad et al., 2001). In childhood, such ERP modulation may potentially serve as convergent evidence in the identification of children at risk of anxiety disorder, before the need for medication arises.

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Appendices

Appendix 1 – Author permission to copy figure 1 (BIS model)

----- Forwarded message from Neil Mc Naughton <nmcn@psy.otago.ac.nz> -----
Date: Mon, 01 May 2006 09:25:24 +1200
From: Neil Mc Naughton <nmcn@psy.otago.ac.nz>
Reply-To: Neil Mc Naughton <nmcn@psy.otago.ac.nz>
Subject: Re: BIS figure
To: elb201@soton.ac.uk

I hereby give Elinor Butterfield permission to use Figures from

J. A. Gray and N. McNaughton. The Neuropsychology
of anxiety: an
enquiry into the functions of the septo-hippocampal system,
(2nd edition) Oxford:Oxford University Press, 2000.

provided full acknowledgment is made of the source in the figure
legends.

neil

Neil McNaughton
Professor of Psychology
University of Otago
Dunedin
New Zealand
FAX: +64 -3- 479 8335

Appendix 2 – Author permission to copy figure 2 The human brain)

Hello,

Sorry for the delay in responding, I was away at a conference.

I have no objection to you using the figure.

Good Luck and please let me know if I can help in any way!

Koraly

(Koraly Perez-Edgar)

----- Original Message -----
From: <elb201@soton.ac.uk>
To: <kpe@umd.edu>
Sent: Saturday, April 08, 2006 4:59 AM
Subject: Request for figure in your Temperament and Anxiety Disorders Paper

Appendix 3 – E-mail confirming University Ethics Committee Approval for the study

Dear Elinor

Re: ERP correlates of anxiety in children

The above titled application was approved by the School of Psychology Ethics Committee on 13 September 2004.

Should you require any further information, please do not hesitate in contacting me. Please quote reference CLIN/03/53.

Best wishes,

Kathryn

Miss Kathryn Smith

Secretary to the Ethics Committee

School of Psychology

University of Southampton

Highfield

Southampton SO17 1BJ

Tel: 023 8059 3995 Fax: 023 8059 2606

Email: kms@soton.ac.uk

Appendix 4 – Parent Checklist

PARENT CHECKLIST

Response to novelty in children

For the purposes of this study we are unfortunately unable to assess children who have a history of any of the following:-

Head Trauma ☐

Neurological Disorder ☐

Psychiatric Disorder ☐

Learning Disability ☐

Hyperactivity ☐

I thank you in advance for your support and co-operation and apologise if your child is unable to take part.

If your child **does not** meet any of the criteria, please complete the consent form only and bring with you on the appointment day.

Thank you

Appendix 5 – Parent Checklist

Developmental Brain-Behaviour Unit
School of Psychology
University of Southampton
Southampton S017 1BJ

Dear Parent or Guardian

We are writing to ask for your permission for your child to take part in a research study looking at childhood personality and the brain's response to sensory stimuli, such as sounds (e.g. a dog bark or a car horn) and faces. There is a brief summary of the study detailed below. If you wish to know more about the study, I can send you further information. Please read the information below and if you do not have any objections to your child taking part, please contact me on **07969 034626**. Thanks in advance for taking the time to read this letter and for returning the form(s).

Yours faithfully

Elinor Butterfield (Trainee Clinical Psychologist).

Personality and Sensory Processing (10.01.05)

What is this study about?

We are interested in normal variations in childhood personality and how this affects the way they may respond to everyday sensory information such as sounds and faces.

Why has my child been invited to take part?

We are asking all parents who have children aged between 10-14 years to take part. We hope this study will help us better understand normal variations in personality in children and how this might influence learning.

What will your child have to do?

We would like to ask you to bring your child to the School of Psychology at the University for a 45 minute appointment. We will ask your child for information about their personality and how they feel at that moment, for example "I feel very calm" or "I feel calm" or "I feel not calm". We will also ask your child to complete some memory games such as repeating a list of words, and pointing to blocks in a certain order.

Following this we would like to place some leads on your child's head in order to look at how their brain processes sounds and pictures (faces). These kinds of stimuli are known to result in a particular pattern of brain activity. The leads are held in place with a watery gel and are not uncomfortable. The project supervisor (Dr Hogan) has over five years experience using this technique with infants and children.

About your child's participation

The project has full ethical approval and we keep all information we collect from your child strictly confidential. We cannot work with your child without your written consent. If you do not have any objections to your child taking part, then please fill out the Consent Form attached and bring it with you to the appointment.

What will happen to the results of the study?

They will be submitted for publication in the scientific literature. Your child's results will be confidential, and we will not identify them by name.

How can I find out more about the study?

A summary of the research project will be supplied to you upon request when the study is completed. To request a project summary or if you have any questions, please contact Elinor Butterfield by email elb201@soton.ac.uk or by telephone on the number above.

Appendix 6a – Child Consent Form

Child's Consent Form

I am looking at the different ways children, like you; react to different sounds.

I need your help to do this project.

All you have to do is answer some questions about the way that you feel. There are no right or wrong answers to the questions.

No-body else, except me, will see any of the answers that you will give.

Some children will then be asked to come to the University to do the next part of the project. They will be asked to listen to some sounds whilst looking at pictures on a computer screen. Not all children will be asked to do this. Do not worry if you are not one of them. We only need a small number for this study and many children will not be asked to do the next part.

It is up to you whether you want to take part or not. I would understand if you decided not to.

Thank you very much.

If you agree to help me, then please sign your name below:

Signature .....

Appendix 6b - Parent Consent Form

CONSENT FORM

***Personality and Sensory Processing in* Children**

Name of Researcher: *Elinor Butterfield*

Name of Child: _____

Child's Date of Birth: _____

Contact Telephone Number for Parent/Guardian: _____

Please initial box

1. I confirm that I have read and understand the information sheet dated (10.01.05) for the above study and am aware that I can contact the researchers to ask questions. ☐
2. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without their legal rights being affected. ☐
3. I agree to allow the researchers named on the information sheet to store anonymised results obtained from my child on a CD disc/ or University computer for up to 15 years after the study has finished. ☐
4. I agree to let my child take part in the above study. ☐

Name of Parent	Date	Parent's Signature

The study has been described to my child by myself, and I am aware that I can gain further information from the researchers if necessary. I am satisfied that at this time my child appears enthusiastic about taking part. I understand, however, that I may withdraw them from the study at any time if I believe they are unhappy.

Name of Parent	Date	Parent's Signature

THANK YOU

Appendix 7 – Copy of the State-Trait Anxiety Inventory for Children (STAIC)

HOW-I-FEEL QUESTIONNAIRE

Developed by C.D. Spielberger, C.D. Edwards, J. Montouri, and R. Lushene

STAIC Form C-1

Name: _____ Age: _____ Date: _____

DIRECTIONS: A number of statements which boys and girls use to describe themselves are given below. Read each statement carefully and decide how you feel *right now.* Then put an X in the box in front of the word or phrase which best describes how you feel. There are no right or wrong answers. Don't spend too much time on any one statement. Remember, find the word or phrase which best describes how you feel right now, *at this very moment.*

1. I feel	☐ very calm	☐ calm	☐ not calm
2. I feel	☐ very upset	☐ upset	☐ not upset
3. I feel	☐ very pleasant	☐ pleasant	☐ not pleasant
4. I feel	☐ very nervous	☐ nervous	☐ not nervous
5. I feel	☐ very jittery	☐ jittery	☐ not jittery
6. I feel	☐ very rested	☐ rested	☐ not rested
7. I feel	☐ very scared	☐ scared	☐ not scared
8. I feel	☐ very relaxed	☐ relaxed	☐ not relaxed
9. I feel	☐ very worried	☐ worried	☐ not worried
10.I feel	☐ very satisfied	☐ satisfied	☐ not satisfied
11.I feel	☐ very frightened	☐ frightened	☐ not frightened
12.I feel	☐ very happy	☐ happy	☐ not happy
13.I feel	☐ very sure	☐ sure	☐ not sure
14.I feel	☐ very good	☐ good	☐ not good
15.I feel	☐ very troubled	☐ troubled	☐ not troubled
16.I feel	☐ very bothered	☐ bothered	☐ not bothered
17.I feel	☐ very nice	☐ nice	☐ not nice
18.I feel	☐ very terrified	☐ terrified	☐ not terrified
19.I feel	☐ very mixed up	☐ mixed up	☐ not mixed up
20.I feel	☐ very cheerful	☐ cheerful	☐ not cheerful

Distributed by MIND GARDEN P.O. Box 60669 Palo Alto California 94306 (415) 424-8493

HOW-I-FEEL QUESTIONNAIRE

STAIC Form C-2

Name: _____ Age: _____ Date: _____

DIRECTIONS: A number of statements which boys and girls use to describe themselves are given below. Read each statement carefully and decide if it is *hardly-ever,* or *sometimes,* or *often* true for you. Then for each statement, put an X in the box in front of the word that seems to describe you best. There are no right or wrong answers. Don't spend too much time on any one statement. Remember, choose the word which seems to describe how you usually feel.

1. I worry about making mistakes..... ☐ hardly-ever ☐ sometimes ☐ often
2. I feel like crying..... ☐ hardly-ever ☐ sometimes ☐ often
3. I feel unhappy..... ☐ hardly-ever ☐ sometimes ☐ often
4. I have trouble making up my mind..... ☐ hardly-ever ☐ sometimes ☐ often
5. It is difficult for me to face my problems.. ☐ hardly-ever ☐ sometimes ☐ often
6. I worry too much..... ☐ hardly-ever ☐ sometimes ☐ often
7. I get upset at home..... ☐ hardly-ever ☐ sometimes ☐ often
8. I am shy..... ☐ hardly-ever ☐ sometimes ☐ often
9. I feel troubled..... ☐ hardly-ever ☐ sometimes ☐ often
10. Unimportant thoughts run through my mind and bother me..... ☐ hardly-ever ☐ sometimes ☐ often
11. I worry about school..... ☐ hardly-ever ☐ sometimes ☐ often
12. I have trouble deciding what to do..... ☐ hardly-ever ☐ sometimes ☐ often
13. I notice my heart beats fast..... ☐ hardly-ever ☐ sometimes ☐ often
14. I am secretly afraid..... ☐ hardly-ever ☐ sometimes ☐ often
15. I worry about my parents..... ☐ hardly-ever ☐ sometimes ☐ often
16. My hands get sweaty..... ☐ hardly-ever ☐ sometimes ☐ often
17. I worry about things that may happen..... ☐ hardly-ever ☐ sometimes ☐ often
18. It is hard for me to fall asleep at night..... ☐ hardly-ever ☐ sometimes ☐ often
19. I get a funny feeling in my stomach..... ☐ hardly-ever ☐ sometimes ☐ often
20. I worry about what others think of me..... ☐ hardly-ever ☐ sometimes ☐ often