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Making the most of ourselves in the 21st century**

**State-of-Science Review: SR-E12
Neurocognition and Neuroimaging in Anxiety Disorders:
Implications for Treatment and Functional Outcome**

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Summary

The term 'anxiety disorders' refers to a collection of mental syndromes characterised by abnormally high levels of distress and avoidance associated with scenarios perceived as dangerous. These syndromes typically arise early in life, can portend life-long patterns of disability, and account for considerable societal costs. Specific anxiety disorders can be distinguished by their unique clinical features, but they also manifest overlapping neuro-cognitive and neuroimaging correlates. After discussing features of specific anxiety disorders, this review goes on to examine neuroscientific approaches to understanding their pathophysiology. Data in animal models delineate a neural circuit that regulates organisms' responses to dangerous situations. In animals, inter-individual variation in the functioning of this circuit, occurring either naturally or following experimental manipulations, predicts inter-individual variation in the processing of threat-related information, impacting on attention, memory, and decision-making. This suggests that humans experiencing high levels of anxiety, such as patients with anxiety disorders, might also exhibit perturbations in attention, memory, and decision-making when confronting real or perceived danger, as well as reduced thresholds for eliciting defensive behaviours. Findings confirm these predictions. Moreover, studies in humans directly link perturbations in the manner in which threats are cognitively processed to dysfunction in specific brain circuitry. This circuitry encompasses the amygdala, ventral prefrontal cortex, and striatum.

1. Introduction

'Fear' refers to the brain state and associated changes in behaviour or cognition occurring when an organism directly confronts a dangerous stimulus or scenario. In contrast to the fear response to immediate danger, 'anxiety' is the brain state following exposure to a 'threat', defined as a cue predicting impending danger, as opposed to the presence of immediate danger. Mammals exhibit strong, stable between-organism variations in the level of fear and anxiety elicited under various circumstances. In humans, these variations are considered manifestations of an 'anxiety disorder' when they either interfere with an individual's ability to function or produce excessive subjective distress.

Anxiety disorders affect approximately one-fifth of individuals and exert profound effects on health and wellbeing (Pine and Klein, 2008). These conditions typically arise early in life, often persist over time, and prospectively predict high risk for many serious mental syndromes, particularly major depressive disorder (MDD), as well as medical illnesses such as cardiovascular and respiratory disease. When they are ongoing, anxiety disorders impact function profoundly: they cause marked personal suffering and produce tremendous loss of human potential through their effects on work or school performance, as well as their impact on social relationships (Pine and Klein, 2008). As a result, from a public health standpoint, anxiety exerts a highly significant adverse impact on wellbeing.

This review begins by summarising key features of anxiety disorders, including their clinical presentation, course, co-morbidity, familial aggregation, and treatment. This summary is followed first by a review of data from animal models and then by a review of the association between clinical anxiety and neuro-cognition. Finally, we summarise the data on the neural substrates of clinical anxiety.

2. Clinical features

Presentations The *Diagnostic and Statistical Manual (DSM-IV-TR)* and *International Classifications of Disease (ICD-10)* recognise more than 10 separate anxiety disorders (American Psychiatric Association 2000;

World Health Organization 2005). While each involves distinct symptoms, questions have arisen about the validity of definitions for specific disorders, given that individual anxiety disorders typically co-occur, and all are characterised by extreme avoidance or distress. A brief description of the seven most frequently studied anxiety disorders follows.

(1) *Specific phobias* involve fears of particular objects or scenarios. These syndromes typically produce relatively minimal impairment and rarely are associated with treatment-seeking unless they are associated with another anxiety disorder (Fyer 1998). (2) *Social anxiety disorder* involves fear of situations where scrutiny from others typically occurs. This condition typically develops in early adolescence, though it shows strong associations with early childhood temperament. Longitudinal studies suggest that adolescent social anxiety disorder predicts high risk for adult MDD (Beesdo et al., 2007). (3) *Post-traumatic stress disorder* (PTSD) develops after a life-threatening trauma and involves fear and hyper-arousal in tandem with avoidance and re-experiencing of trauma-related themes. This syndrome shows particularly broad associations with diverse other mental syndromes, including other anxiety disorders, as well as mood, behavioural, and substance-use disorders (Yehuda, 2002). (4) *Panic disorder* involves short-lived paroxysms of extreme anxiety and autonomic arousal that arise spontaneously, without an obvious cue. Over time, a subset of individuals with panic disorder develops agoraphobia, a fear of situations, such as crowded rooms or elevators, from which escape is difficult. Agoraphobia can predict a relatively poor prognosis (Klein, 1996). Panic disorder virtually never develops before puberty, though it has been linked in family studies to (5) *Separation anxiety disorder*, a condition typically manifest in pre-adolescent children as excessive fear concerning the potential for harm to an attachment figure (Pine and Klein, 2008). (6) *General anxiety disorder* (GAD) involves recurrent worries about many aspects of life, in association with cognitive and somatic complaints. GAD exhibits particularly robust associations with other anxiety disorders, MDD and neuroticism, a facet of personality. Twin studies suggest that GAD and MDD show complete genetic overlap, partially through relationships with neuroticism (Hettema et al., 2001).

Some disagreement persists over the classification of (7) *Obsessive-compulsive disorder* (OCD) as an anxiety disorder. OCD is included as an anxiety disorder in DSM-IV-TR but not in ICD-10. It is characterised by a pattern of obsessions or compulsions. Obsessions involve recurrent, intrusive, anxiety-provoking thoughts, ideas, or images about specific qualities (e.g. cleanliness, religiosity, symmetry), whereas compulsions involve thoughts or behaviours (e.g. cleaning, praying, re-arranging), designed to reduce these obsessions. This syndrome differs from other anxiety disorders in terms of its particularly strong associations in longitudinal and family-genetic studies with movement disorders (e.g. tics and Tourette's Syndrome) and attention-deficit hyperactivity disorder (ADHD), consistent with evidence implicating basal ganglia dysfunction in this family of syndromes (Rosenberg and Hanna 2000; Chamberlain et al., 2005).

Life-course presentation Adult anxiety disorders typically develop in individuals suffering from pediatric anxiety. Initial signs of risk for anxiety can manifest in infancy as 'behavioural inhibition', a stable temperament profile involving wariness when confronting novelty (Fox et al., 2005). Inhibition occurs equally commonly in girls and boys, whereas anxiety disorders show a strong female preponderance, suggesting that sex moderates the transition from temperament to disorders. Anxiety disorders are common throughout life but show changing manifestations with development (Pine and Klein 2008). Whereas separation anxiety disorder is most common before adolescence, social anxiety disorder, panic attacks and GAD become more common following puberty. PTSD exhibits wide variations across environmental contexts, according to the amount of traumatic exposure. OCD exhibits one peak period of onset in childhood and a second peak closer to adulthood (Rosenberg and Hanna, 2000).

Most adult anxiety disorders develop in individuals with pediatric anxiety, but most children with anxiety disorders remit. This raises major questions about the processes distinguishing children with transient as opposed to chronic anxiety. While not all evidence is consistent, most studies find that any one of the various pediatric anxiety disorders confers risk for adult anxiety disorders, with minimal evidence that

narrowly defined disorders exhibit unique courses. Anxiety disorders, manifest in adulthood, generally wax and wane in clinical severity. While few adults remain symptom-free throughout life, few suffer complete incapacity due to their anxiety.

Familial aggregation Anxiety disorders aggregate strongly within families. Most studies find broad associations among a range of such disorders (Hettema et al. 2001). For example, children born to parents with panic disorder face an elevated risk for a range of anxiety disorders as opposed to one specific disorder. Exceptions to this pattern do arise. For example, OCD and specific phobia aggregate most strongly with OCD and specific phobia, respectively, as opposed to other anxiety disorders (Fyer 1998; Rosenberg and Hanna, 2000). Twin and adoption studies suggest that non-shared environmental factors (that is, factors which tend to differentially influence risk in members of the same family) account for most of this aggregation, followed closely by genes and gene-environment interactions.

Relatively few studies examine the role of specific genes in anxiety disorders. Candidate gene studies focus on relevant neurochemical and neurohormonal systems implicated in animal models of anxiety (Pine and Klein, 2008). These studies find some relationship between risk for anxiety and the genes involved in regulating the monoamines serotonin (5HT), noradrenaline, and dopamine, as well as the hypothalamic-pituitary-adrenal (HPA) axis. Nevertheless, the magnitude of association is small, consistent with polygenetic influences on risk for anxiety. Some researchers suggest that stronger relationships might exist between genes and functional aspects of the underlying neural circuit implicated in anxiety, centered on amygdala-prefrontal cortex (PFC) connections (Pezawas et al., 2005).

Treatment Two treatments effectively reduce virtually all forms of anxiety at all ages (Pine and Klein, 2008). First, while various medications show some efficacy, the data appear strongest for the selective serotonin re-uptake inhibitors (SSRIs), implicating serotonin (5-hydroxytryptamine – 5HT) in anxiety. Second, cognitive behavioural therapy (CBT) is also effective in anxiety. CBT relies on principles derived from research on fear conditioning and extinction. This work suggests that exposure to fear cues, in the absence of traumatic experience, dissipates fear and anxiety. As such, the efficacy of CBT indirectly implicates fear conditioning in anxiety.

For both treatments, applicability across diverse anxiety states suggests that anxiety disorders share underlying biological mechanisms. Finally, while both treatments are effective, neither produces remission in most patients, emphasising the need for more research in therapeutics.

3. Animal models of anxiety

Fear conditioning Fear conditioning occurs after a neutral conditioned stimulus (CS+), such as a tone or a light, has been paired with an aversive unconditioned stimulus (UCS), such as a shock, leading the CS+ to elicit physiological and cognitive responses associated with the UCS. These changes are mediated by a precisely-defined 'fear circuit' centered on the amygdala, a bilateral collection of medial temporal lobe nuclei (LeDoux, 2000).

Clinical interest in fear conditioning reflects strong cross-species parallels. Across mammalian species, parallel relationships emerge between amygdala-based changes and changes in physiology or cognition. These parallels, coupled with precise knowledge of molecular underpinnings, generate hypotheses on the role of fear conditioning in anxiety disorder pathophysiology and treatment.

During fear conditioning, organisms also develop fear of the spatial and temporal context in which conditioning occurs, through interactions between the amygdala and other components of the fear circuit. Thus, following conditioning, organisms come to fear both the specific CS+ as well as more general features of the spatial environment in which conditioning occurs, a process that requires the hippocampus (LeDoux, 2000).

Similarly, organisms learn the temporal context of conditioning through the engagement of the ventral and medial prefrontal cortex (PFC). For example, following extinction, the CS+ is treated as an ambiguous stimulus that previously was more dangerous than it is in the present (Bouton, 2002). Thus, extinction requires a PFC-based representation of the specific time frame during which conditioning and extinction both occur, consistent with a broad role for PFC-based representations in behaviour regulation.

Response to innate danger Work on unlearned fear also is clinically relevant, given that many anxiety disorders involve excessive fear of innate dangers that arise in patients with no recollection of adverse prior experience with these dangerous stimuli. While organisms learn to fear some stimuli through conditioning, others are feared innately.

The circuitry underlying these two types of fear can be distinguished. Specifically, while fear of a CS+ requires engagement of the central nucleus of the amygdala (CAE), some innate fears persist after CAE lesions (Davis, 1998). For example, the rat, a nocturnal organism, exhibits an innate fear of a well-lit, open field which persists after CAE lesions. In contrast, lesions to the bed nucleus of the stria terminalis disrupt this innate fear but not fear of a CS+. Other work, relying on genetic manipulations, demonstrates similar dissociations of the neural architecture underlying learned and innate fears. Given cross-species parallels, the circuitry mediating human fears is also likely to be heterogeneous.

Development During development, fear and anxiety are shaped by genetic and environmental events. In terms of genes, manipulations of the rodent 5HT system produce robust changes in anxiety, with some of these effects being modulated by development (Gross and Hen, 2004). Similar developmental findings emerge for environmental effects (Meaney, 2001). For example, manipulations of the rodent rearing environment within the first weeks of life produce longstanding changes in anxiety-related behaviours through effects on DNA methylation. Studies in non-human primates demonstrate comparable developmental modulation (Gross and Hen, 2004).

4. Cognition and anxiety

Reaction to innate threats Experimental studies in humans consistently show that anxiety disorders involve reduced thresholds for engaging defensive behaviours and associated cognitions when confronting threat cues (Pine, 2007). These findings emerge with diverse indicators of defensive responding, including subjectively-reported states, levels of autonomic arousal, measures of cognition, and indicators of avoidance behaviour. The most consistent findings emerge when patients are presented with innately dangerous stimuli in the laboratory.

In this work on response to innate threats, some evidence of disorder-specificity emerges. For example, patients with panic disorder and separation anxiety disorder, but not patients with social anxiety disorder, respond with extreme anxiety and physiological arousal to situations that involve subtle cues of impending suffocation. The opposite applies for exposure to social threats, where patients with social anxiety but not panic or separation anxiety disorder respond with extreme anxiety (Pine, 2007). Findings in panic disorder have been attributed alternatively to specific hypersensitivity to respiratory threats or to a broader susceptibility to diverse situations involving autonomic arousal (Klein, 1996). Whatever the explanation, the findings indicate a relatively specific connection between panic disorder and enhanced sensitivity to autonomic arousal.

Similarly, patients with OCD exhibit abnormal responses to disorder-relevant cues, such as presentations of dirty or asymmetric objects (Rosenberg and Hanna, 2000). However, for other threats, such as non-specific threats of impending physical discomfort, patients with various anxiety disorders show enhanced responses, with no differences among the disorders (Pine, 2007).

Attention In another set of consistent findings, threat presentation has been shown to exert differential effects on attention in healthy subjects *versus* those with, or at high risk for, anxiety disorders (Bar-Haim et al., 2007). Robust effects consistently emerge on attention-orienting paradigms, where patients with anxiety (or subjects who score high on anxiety trait scales) exhibit a reduced threshold for attention-orienting to mild threats and attention avoidance of more extreme threats.

Robust effects also have been demonstrated on attention-interference paradigms i.e. threats exert greater interference on competing, non-emotional tasks, such as colour-naming, in anxiety patients or at-risk individuals, than in healthy subjects. Unlike the response to innate threats, the weight of the evidence suggests that anxiety-linked attention perturbations emerge across the anxiety disorders, with limited evidence of disorder specificity.

Memory and learning Inconsistent findings emerge from research on the associations between anxiety disorders and deficits in memory and learning.

One set of theories suggests that threats influence memory more strongly in anxiety disorders than in healthy individuals. However, the weight of the evidence finds only weak patient-control differences in memory for most anxiety disorders, with the exception of PTSD (Macleod and Mathews, 2004). In PTSD, the evidence more readily implicates memory perturbations, consistent with hippocampal involvement in both PTSD and declarative memory (Bremner, 2006).

A second set of theories suggests that OCD is associated with perturbations on implicit memory tasks that involve non-threatening materials (Chamberlain et al., 2005). Such deficits are expected, given the data implicating fronto-striatal circuitry in both implicit learning and OCD.

The data appear inconsistent for studies of fear conditioning (Lissek et al., 2005). Interest in clinical correlates of fear conditioning follows from work on CBT, suggesting that individual differences in fear conditioning account for individual differences in vulnerability for clinical anxiety disorders. Inconsistent with these views, however, patients with anxiety disorders typically exhibit normal fear conditioning. To the extent that fear conditioning abnormalities exist in anxiety disorders, they appear relatively subtle. In light of these data, coupled with the indisputably strong evidence of CBT efficacy, current theories suggest that anxiety disorders involve deficiencies in the extinction of fears more than in fear conditioning acquisition (Bouton, 2002), with CBT reducing anxiety through facilitation of extinction.

Decision-making and cognitive control Cognitive neuroscience studies implicate connections between the PFC and striatum, (so-called 'fronto-striatal circuitry') in regulating behaviour when organisms confront decisions in the context of competing goal demands. In these situations, 'cognitive control' refers to a suite of mental capacities that allow organisms to weigh alternative behavioural choices and flexibly choose, from among diverse behaviours, the specific act most consistent with current goals (Miller and Cohen, 2001).

Because motivational factors influence decision-making, and because activity in fear circuitry influences activity in fronto-striatal circuitry, some suggest that clinical anxiety involves perturbed cognitive control. Various experimental paradigms have been used to compare cognitive control in healthy individuals, patients with anxiety disorders, and those with other psychopathology. These include variations of Go/No-go tasks, the flanker paradigm, and the stop task. However, as with research on memory, most studies find intact cognitive control in patients with anxiety disorders, although a noticeable exception occurs in OCD, where patients consistently show deficient cognitive control (Chamberlain et al., 2005).

Patients with ADHD also exhibit deficient cognitive control on these tasks, consistent with data from longitudinal and family studies distinguishing OCD from non-OCD anxiety disorders based on similarities among OCD, ADHD and movement disorders.

5. Neural substrates of clinical anxiety

Brain structure Recent structural imaging studies delineate the degree to which distinct anxiety disorders are associated with alterations in amygdala-based or fronto-striatal circuitry. Data are most consistent in adults with PTSD, where a wealth of studies document reduced hippocampal volume and medial PFC volume (Bremner, 2006). Interestingly, these data in adults show both similarities and differences with the data for juveniles, where PTSD has been linked to perturbed medial PFC but intact medial temporal structures.

Data on brain morphometry in OCD are less consistent than in adult PTSD (Rosenberg and Hanna, 2000). While abnormalities in ventral PFC, amygdala, and striatum have been demonstrated, these findings are inconsistent, with reports of enlarged, reduced, and normal volumes. Similarly inconsistent findings emerge in other anxiety disorders, both among adults and juveniles (Pine, 2007). While some brain morphometry data implicate the amygdala and PFC, the inconsistencies across studies are as notable as the consistencies.

Studies of patients with brain lesions or illnesses provide further clues linking perturbed brain structures to anxiety. Here, the most consistent evidence emerges from studies of patients who develop OCD secondary to a brain lesion or illness, where basal ganglia pathology is implicated consistently (Rosenberg and Hanna, 2000). Similarly, patients with lesions in ventral expanses of the PFC consistently show signs of reduced anxiety (e.g. social disinhibition), thereby implicating these areas in anxiety disorders. Interestingly, however, patients with amygdala or hippocampal lesions show surprisingly few of the core alterations in behaviour or cognition associated with anxiety disorders.

Functional imaging Emerging functional imaging data generate relatively consistent conclusions across age groups for a range of anxiety disorders. Thus, studies consistently implicate the hippocampus and the amygdala, as well as the ventral and medial PFC, in PTSD (Rauch and Shin, 2003). Much imaging work relies on paradigms in which patients are exposed to traumatic reminders in order to engage clinically relevant emotional states. Similarly, brain imaging research on OCD reveals consistent abnormalities in fronto-striatal circuitry, across studies of resting metabolism, the neural response to disorder-relevant cues, and neural processes engaged in cognitive control or implicit learning tasks (Rosenberg and Hanna, 2000).

Finally, studies in adults with social phobia and in young people with anxiety disorders yield similar results. Much of this work uses paradigms in which research participants are exposed to faces of varying emotional valences (Pine, 2007). These studies generally find that patients exhibit a lower threshold than healthy subjects for engaging the amygdala or the ventral PFC when exposed to negative-valence faces. Moreover, findings implicate the amygdala in risk for anxiety. Adolescents without an anxiety disorder but with an early-childhood history of behavioural inhibition, as well as those with an anxiety disorder, exhibit amygdala hypersensitivity on the same paradigms (Pine, 2007). Such amygdala hypersensitivity does not occur in OCD, providing some support for distinguishing OCD from other disorders.

Neurochemistry Studies in animal models provide targets for research on neurochemistry. Such research is directly relevant for therapeutics, since pharmacologic interventions can modulate fear-circuitry function. While diverse systems have been investigated, data appear most consistent for three brain systems.

First, considerable work implicates perturbed HPA axis function in anxiety disorders, consistent with work in animal models (Gross and Hen, 2004; Bremner, 2006; Pine and Klein, 2008). High state and trait anxiety are associated with elevated HPA axis responses to stressors. PTSD is also consistently associated with HPA axis abnormalities, although the direction of these findings varies; most, but not all, studies report enhanced feedback regulation. Consistent with these data, pharmacologically augmenting HPA axis activity in adults with PTSD appears to decrease symptoms. Similarly, psychotherapy in young children at risk for PTSD is associated with both decreased symptoms and HPA axis elevations (Brotman et al., 2007). As with other findings noted above, these data demonstrate distinctions between PTSD and other anxiety disorders.

Second, a considerable body of work implicates 5HT in anxiety states (Gross and Hen, 2004). Probably the strongest evidence derives from the efficacy of the SSRIs. Other work uses positron emission tomography (PET) to demonstrate perturbations in various 5HT receptor densities in patients with panic disorder, PTSD or OCD. However, none of these findings has been well-replicated, and their direction has varied across PET ligands, brain region, and specific anxiety disorder. Neuroendocrine challenge studies and studies of cerebrospinal fluid (CSF) metabolites also note signs of perturbed 5HT function in panic disorder, PTSD or OCD, but, once again, the nature of these findings varies across experimental approaches and specific disorders.

Finally, the noradrenaline (NA) and dopamine (DA) systems have been implicated in anxiety disorders, though evidence is weaker than for 5HT (Pine and Klein, 2008). Evidence of NA involvement emerges in therapeutics, where NA medications treat panic disorder, PTSD and GAD, though, interestingly, not social phobia or OCD, which instead show stronger responses to DA medications. As with studies of 5HT, evidence implicating NA or DA in anxiety emerges from studies of CSF metabolites, response to pharmacological probes, and the few available studies using relevant PET ligands.

6. Conclusions

The importance of work on anxiety derives from the high prevalence of clinical anxiety and the significant negative impact of anxiety disorders on wellbeing.

This negative impact arises at least partially from effects in a significant group of individuals who manifest persistent anxiety and an association with major depressive disorder across the lifespan.

Thus, a subgroup of children manifesting early-life anxiety will mature to become adults with chronic anxiety and mood disorders, accounting for a large mental health burden facing society.

Work in animal models demonstrates strong, cross-species parallels in the neural circuitry mediating anxiety.

Advances in translational neuroscience have begun to delineate the manner in which individual differences in humans reflect variations within this same neural circuitry.

As these advances continue, such insights are likely to give rise to novel treatments that hold the hope of reducing the major burden resulting from chronic anxiety.

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