Available online at www.sciencedirect.com
SCIENCE DIRECT
Neuroscience and Biobehavioral Reviews 30 (2006) 511–525
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
www.elsevier.com/locate/neubiorev

Review

The neurobiological basis of temperament: Towards a better understanding of psychopathology

Sarah Whittle [a,b], Nicholas B. Allen [a,b,*], Dan I. Lubman [a,c,d], Murat Yücel [a,c,d]

[a] *ORYGEN Research Centre, University of Melbourne, Vic. 3052, Australia*
[b] *Department of Psychology, University of Melbourne, Vic. 3010, Australia*
[c] *Department of Psychiatry, University of Melbourne, Vic. 3010, Australia*
[d] *Melbourne Neuropsychiatry Centre, University of Melbourne, Vic. 3053, Australia*

Received 17 March 2005; received in revised form 7 September 2005; accepted 13 September 2005

Abstract

The ability to characterise psychopathologies on the basis of their underlying neurobiology is critical in improving our understanding of disorder etiology and making more effective diagnostic and treatment decisions. Given the well-documented relationship between temperament (i.e. core personality traits) and psychopathology, research investigating the neurobiological substrates that underlie temperament is potentially key to our understanding of the biological basis of mental disorder. We present evidence that specific areas of the prefrontal cortex (including the dorsolateral prefrontal, anterior cingulate, and orbitofrontal cortices) and limbic structures (including the amygdala, hippocampus and nucleus accumbens) are key regions associated with three fundamental dimensions of temperament: Negative Affect, Positive Affect, and Constraint. Proposed relationships are based on two types of research: (a) research into the neurobiological correlates of affective and cognitive processes underlying these dimensions; and (b) research into the neurobiology of various psychopathologies, which have been correlated with these dimensions. A model is proposed detailing how these structures might comprise neural networks whose functioning underlies the three temperaments. Recommendations are made for future research into the neurobiology of temperament, including the need to focus on neural networks rather than individual structures, and the importance of prospective, longitudinal, multi-modal imaging studies in at-risk youth.

Keywords: Temperament; Personality; Neurobiology; Neural network; Psychopathology; Mental illness; Emotion regulation; Negative affectivity; Positive affectivity; Constraint; Prefrontal cortex; Amygdala; Inhibition

Contents

* Corresponding author. Tel.: +61 3 8344 6325; fax: +61 3 9342 6618.
E-mail address: nba@unimelb.edu.au (N.B. Allen).

0149-7634/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2005.09.003

There is a large body of neuropsychiatric research demonstrating that a number of psychiatric conditions are accompanied by significant neurobiological abnormalities. An overview of this literature reveals that such abnormalities (observed both within and across these disorders) are generally inconsistent or non-specific, yielding attempts to cleanly delineate disorders and/or sub-groups on the basis of neurobiology unsuccessful (Davidson et al., 2002a,b). These findings are not surprising given that comorbidity and heterogeneity are commonly encountered in the current categorical diagnostic system. As quoted in a recent publication outlining a research agenda for the DSM-V:

> The field of psychiatry has thus far failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder or for predicting response to psychopharmacologic treatment…[It will be an achievement for psychiatry to move into the] mainstream of modern medicine, where etiology and pathophysiology have replaced descriptive symptomatology as the fundamental basis for making diagnostic distinctions (Kupfer et al., 2002).

This statement highlights the need for a more objective approach to the characterisation of psychopathology, possibly one that is parsimonious with underlying neural circuitry, for a better understanding of mental disorder. We suggest that one such approach may be on the basis of core dimensions of temperament.

The term temperament refers to endogenous basic tendencies of thoughts, emotions, and behaviour. There is general consensus that temperamental dimensions are observed in infancy, are genetically influenced, and are modestly but significantly preserved across the lifespan. Although temperament as a concept has been around for 2000 years, dating back to the Greeks (Kagan, 1994), the empirical studies of Chess and Thomas over 40 years ago (Chess et al., 1960) sparked a resurgence of interest in infant temperaments. Two fundamental temperaments described by Chess and Thomas are related to typical responses to unfamiliar people, objects, and situations. They describe infants who tend to approach the unfamiliar as *uninhibited*, and infants who tend to avoid the unfamiliar as *inhibited*. These two dimensions have been extensively studied and reliably identified in both children and adults (Clark and Watson, 1999; Clark et al., 1994; Kagan, 1996).

A third fundamental temperament factor, Effortful Control, has since been suggested by Rothbart and colleagues (Rothbart et al., 2003), and is described as the ability to suppress a dominant response in order to perform a subdominant response. That is, Effortful Control allows one to suppress affect driven motivational and behavioural tendencies and to re-program behaviour in conflictual situations. There is evidence that this factor may not be present in early infancy, but emerges and develops from around the age of three, and is an outcome of the development of executive control of attention. Rothbart and colleagues (Rothbart et al., 2003) cite a number of studies finding links between low Effortful Control and the development of aggression, externalising behaviours, and substance use in adolescence.

There is some disagreement about the relationship between temperament and personality. Some argue that they are the same construct. Others argue that temperament is a lifelong, yet distinct component of personality (Cloninger, 2000). Others propose that temperaments form the core around which broader personality traits develop (Clark et al., 1994). Most research points to a high degree of overlap between these constructs, especially when considering adolescents and adults, which has lead many to conclude that the distinction is more historical than substantive (Rettew and McKee, 2005).

Several models of adult personality including Eysenck's three factor model (Eysenck, 1967), Clark and Watson's three factor model (Clark and Watson, 1999), Tellegen's system of personality structure (Tellegen, 1985), and Cloninger's temperament model (Cloninger, 1986), appear to have common three higher-order dimensions that essentially reflect the three temperamental dimensions described above. From this point on we will refer to these three temperamental dimensions as Negative Affectivity (NA), Positive Affectivity (PA), and Constraint. Inhibition, avoidance and punishment sensitivity are heightened in individuals high on NA. These individuals have a propensity to experience a wide range of negative moods such as fear, anxiety, sadness, and guilt. Individuals high on PA have an active engagement in the world through high approach and reward sensitivity, and have a propensity to experience a wide range of positive moods such as joy, happiness, enthusiasm, and pride. Constraint refers to an individual's degree of control over

impulses and emotions, their ability to direct attention and delay gratification. Individuals high on this dimension may be described as diligent, persistent, reliable, and responsible.

Note that while NA, PA, and Constraint have been identified as equivalent, independent factors, there is suggestion that Constraint (unlike NA and PA) is non-affective but interacts with NA and PA by influencing the links between stimuli and response (i.e. it influences the amount of control one has over approach and withdrawal tendencies) (Depue and Collins, 1999). There is evidence that NA has moderate negative correlations with Constraint, and as mentioned, Constraint appears to emerge later in development (Rothbart et al., 2003).

We base our premise that temperament may provide a fruitful method for objectively characterising psychopathologies on two lines of research, which are discussed in more detail below. Firstly, there is a widely held view that temperament is strongly related to most psychopathologies, especially those involving affective disturbance. Secondly, there is accumulating evidence that temperamental dimensions have roots in separate neurobiological systems, and these systems appear to be similar to those that have been associated with various psychopathologies.

1. Core affective dimensions and psychopathology

Recent work on the underlying structure of psychopathological symptoms has revealed that the fundamental dimensions of symptomatology thematically resemble the underlying structure of temperament description. Krueger (1999), in a study of ten common mental disorders, found a three-factor model to provide the best fit to the pattern of comorbidity among symptoms in a national probability sample of 8098 US civilians. The first factor, which the authors name *externalising*, was indicated by Alcohol Dependence, Drug Dependence, and Antisocial Personality Disorder (APD). The second and third factors, named *anxious-misery* and *fear*, were two highly correlated sub-factors of a higher order factor named *internalising*. The *anxious-misery* factor was formed by Major Depression (MD), Dysthymia, and Generalised Anxiety Disorder (GAD), and the *fear* factor was formed by Panic Disorder (PD), Agoraphobia, Social Phobia and Specific Phobia. These three factors are described by the authors as referring to broad but coherent spectra of personality and psychopathology.

There is considerable evidence of significant and stable relationships between the three temperaments NA, PA, and Constraint (as measured by self-report questionnaire) and several mental disorders in adolescence and adulthood (see reviews by Clark et al., 1994; Rettew and McKee, 2005; Watson et al., 2005). NA appears to be a general predictor of psychopathology, and has been particularly linked with mood and anxiety disorders. However, it is more strongly associated with disorders characterised by pervasive distress (e.g. MD and GAD) than with disorders involving more limited forms of distress (e.g. Social Phobia and PD), or characterised primarily by behavioural avoidance (e.g. Specific Phobia and Agoraphobia). Clark and Watson (1999) term PA a depression specific factor, in that while high NA is a key feature of both mood and anxiety disorders, PA reliably distinguishes the two, with low PA present in mood disorders, but not in anxiety disorders. Others have suggested, however, that low PA is a feature of some anxiety disorders, such as Social Phobia (Watson et al., 2005). Note that most of the research linking temperament with mood disorder has focused on unipolar depression. Studies focusing on Bipolar Disorder (BD) have been mixed in finding associations with both NA and PA (Rettew and McKee, 2005). Substance Use Disorders (SUDs) and antisocial disorders appear to be best characterised by high NA and low Constraint (Krueger, 1999; Livesley et al., 1998; Swendsen et al., 2002). It has been suggested, however, that there may be a high PA type of SUD, in which individuals seek to enhance levels of PA (Widiger et al., 1999). Further, low NA may characterise some antisocial disorders marked by more predatory aggression and premeditated rule-breaking (Watson et al., 2005). See Table 1 for a summary of main psychopathologies discussed and their corresponding temperamental characteristics.

Table 1
Summary of relations between psychopathology and temperament

	Negative affectivity	Positive affectivity	Constraint
Mood disorders (+GAD)	↑↑[a]	↓↓	
Anxiety disorders	↑	↓[b]	
Substance use disorders	↑	↑[c]	↓↓
Antisocial disorders	↑ or ↓[d]		↓↓

[a] Double arrows indicate stronger relationships.
[b] Some anxiety disorders have been associated with low PA, such as Social Phobia.
[c] In a high PA type of SUD, individuals seek to enhance levels of PA rather than reduce levels of NA.
[d] Low NA is seen in some antisocial disorders marked by predatory agression and rule-breaking.

Several alternative models of the relationship between temperament and psychopathology have been proposed (note, however, that these models are probably not mutually exclusive). *Vulnerability* or *pathoplasty* models propose temperament plays a causal role in psychopathology, either by increasing the likelihood of developing psychopathology or by affecting the course or the severity of disorder, respectively. *Complication* or *scar* models state that psychopathology alters temperament either temporarily or permanently. *Spectrum* models state that both temperament and psychopathology reflect the same underlying process such that psychopathologies are extreme manifestations of normal temperamental dimensions. Most of the available evidence supports the *pathoplasty*, *complication*, and *scar* models (see Clark et al., 1994). There are some prospective, longitudinal studies, however, that provide evidence for *vulnerability* and *spectrum* models. For example, in a pioneering longitudinal study, Schwartz and colleagues (Schwartz et al., 1999) tracked 79 adolescents who had been characterised by Kagan 12 years previously, in the second year of life, as inhibited or uninhibited. They reported an association between early inhibited temperament and later generalised social anxiety (uninhibited temperament appeared to protect adolescents from

social anxiety), demonstrating the role of temperament as a vulnerability factor for the emergence of psychopathology.

2. Neurobiological underpinnings of core affective dimensions

The idea that temperament is grounded in biology has been around for many decades. Eysenck (1967) was a pioneer in attempting to relate temperament to individual differences in cortical arousability. Gray (1983, 1994), using data about brain systems that are known to be involved in emotions, learning, memory, and motor behaviour, developed a comprehensive model describing how individual differences in temperament are produced by differences in the relative activity within and interactions between three emotional brain systems: the Behavioural Inhibition System (BIS), the Behavioural Activation System (BAS), and the Fight-Flight System (FFS). Depue and Collins (1999) and Cloninger (1986, 2000) have also proposed theories of specific brain systems underlying individual differences in temperament. However, to date, there has been very little neurobiological research supporting these theories. The bulk of research to date has focussed on neurophysiology, neurochemistry and molecular genetics (see Cloninger, 2000, for a review) with only a few studies empirically examining the structural and functional brain correlates of temperamental dimensions using brain imaging techniques. A few attempts have been made to relate temperament to brain function using measures of brain activity such as blood flow or glucose metabolism (Johnson et al., 1999; Sugiura et al., 2000; Turner et al., 2003; Youn et al., 2002). Results have been promising in that the dimensions assessed appear to correlate with the activity of many of the brain structures proposed in earlier neurobiological models. However, findings have not been entirely consistent, and discrepancies have been noted in activity levels (i.e. reports of increased or decreased activity) within the same brain structures. Comparisons across these studies are difficult, as the temperamental dimensions assessed have been measured by different instruments. Indeed, it is not entirely clear how dimensions measured by different instruments might map onto one another.

There have been some studies looking at the structural correlates of temperamental dimensions using volumetric or morphometric shape measurements (Knutson et al., 2001a,b; Matsui et al., 2000; Pujol et al., 2002), but too few to enable strong conclusions to be drawn. Further, these studies have taken very gross volumetric measures (such as whole brain or whole frontal lobe volume), failing to acknowledge the contribution of cytoarchitectually distinct cortical areas. No temperament study has yet looked at the structure of subcortical brain structures.

While these few studies have made important contributions to our understanding of the neurological basis of temperament, there is still much we do not know. Most studies have been exploratory rather than theory driven and all have been with adults. While the early neurobiological models of temperament provide useful frameworks for making predictions about how individual differences in temperament might be explained by activity in specific brain systems, given the strong links between temperament and psychopathology, and between psychopathology and brain abnormality, more comprehensive models that incorporate our knowledge of these links may be more useful in making such predictions.

One notable recent study has attempted to relate our knowledge of the link between temperament and brain functioning to psychopathology. Schwartz and colleagues (Schwartz et al., 2003) found that adults who had been categorised in the second year of life as inhibited, compared with those previously categorised as uninhibited, had a greater response within the amygdala to novel versus familiar faces. Interestingly, three of the fifteen adults categorised as inhibited in the second year of life were diagnosed with social phobia, whereas none of the uninhibited subjects had anxiety disorders as adults. These results suggest that discovered differences in brain activity between patients with psychopathology and controls should not always be regarded as specific markers of the disorder, but may instead reflect a temperamental risk factor, or diathesis, for the diagnostic category under study. Studies such as this have the potential to better characterise the underlying neural circuitry related to temperamental traits and the psychopathological states that emerge from them.

3. Underlying neural circuitry of core affective dimensions and psychopathology

In the remainder of this review, a model will be proposed that describes the hypothesised relationship between three core temperamental dimensions NA, PA, and Constraint, and six key interconnected brain regions. The brain structures that we conjecture to be associated with these temperamental dimensions have been selected on several grounds. Firstly, they have all been implicated in at least one of the aforementioned neurobiological models of temperament. Secondly, they have all been associated with various kinds of affective and cognitive processing understood to underlie individual differences in temperament. Thirdly, they have all been implicated in those psychopathologies that have been related to temperamental factors, and prominently involve affective disturbance. The six structures include the amygdala, hippocampus, Nucleus Accumbens (NAcc), Orbitofrontal Cortex (OFC), Anterior Cingulate Cortex (ACC), and the Dorsolateral Prefrontal Cortex (DLPFC). The following review covers human studies looking at function as indexed by blood flow, glucose metabolism, or perfusion, and structure as indicated by measurements of simple volume or complex morphometry (such as shape differences). Brief mention is also given to neurochemical studies, although neurochemical models are not the focus of this review. Note that the number of brain structures likely to be associated with temperament is far greater than the six we propose here. A number of other subcortical structures (e.g. hypothalamus and periadequctal gray) are particularly likely to be involved, but are excluded from the discussion because most of the related research comes from animal studies, which are more difficult to assimilate with the human literature.

3.1. Negative affectivity, and the amygdala

There is a substantial amount of research documenting the structural and functional brain correlates of NA. There is robust empirical evidence supporting a relationship between NA and the structure and function of subcortical structures including the amygdala and hippocampus, and prefrontal structures including the ACC and right DLPFC.

The amygdala is thought to participate in the initial and largely subconscious assignment of affective significance to sensory events (LeDoux, 1993; Ochsner and Schacter, 2000). Much research has implicated the amygdala in the perception and production of negative affects and associative aversive learning (Adolphs and Damasio, 2000; Davidson and Irwin, 1999; Davidson et al., 2000; Ochsner and Schacter, 2000).

In healthy individuals, functional studies have documented increased amygdala activation during exposure to unpleasant stimuli (see Zald, 2003 for a review) and during the production and maintenance of negative affects (Davidson et al., 1999; Schaefer et al., 2002). Also, activation at rest has been found to predict the severity of trait NA, as assessed through questionnaire (Davidson and Henriques, 2000). The amygdala has been ascribed a central role in the detection of threat and the production of fear and anxiety states, with greater activation observed during the presentation of fearful compared to neutral or happy stimuli (Schwartz et al., 2003). There is increasing evidence to suggest however, that the amygdala's role in processing fear and other aversive states stems from its broader role in responding to novelty (i.e. detecting, processing and integrating stimuli that have potential biological importance), of which threat is only one possible example (Whalen, 1998). As mentioned in the introduction, Schwartz et al. (2003) found that adults with an early inhibited compared to uninhibited temperament showed greater amygdala response to novel versus familiar faces.

Increased activation of the amygdala has been a consistent finding in the resting state of patients with high NA related disorders, particularly anxiety disorders such as obsessive compulsive disorder (OCD), panic disorder, and post-traumatic stress disorder (PTSD) (Drevets, 1999).

The size of the amygdala has also been correlated with measures of NA. In one study of epilepsy patients, amygdala volume was found to correlate positively with a self report measure of dysthymia (Tebartz van Elst et al., 1999). Structural imaging studies of mood, anxiety, and BPD patients have documented both increased and decreased amygdala volumes. Increased volume however, has usually been found in first episode or early onset patients (De Bellis et al., 2000; Sheline, 2000), while decreased volume has usually been reported in individuals who are older, have longer illness durations, or have had recurrent episodes (Frodl et al., 2003; Schmahl et al., 2003; Tebartz van Elst et al., 2003), suggesting increased volume might be associated with a vulnerability to disorder (e.g. high NA), whereas reduced volume might occur as a progressive consequence of the disorder.

3.1.1. The hippocampus

The hippocampus has a long established role in spatial processing and certain forms of memory. However, it has become increasingly apparent that the hippocampus plays a more general role in information processing and behavioural regulation, and that these various functions may be distributed through the hippocampus. Based mainly on evidence from animal studies, it has been recently suggested that there are two main subregions of the hippocampus: a dorsal region that has a preferential role in spatial learning and memory, and a ventral region that has a preferential role in anxiety related behaviours (Bannerman et al., 2004).

This suggestion is in agreement with Gray's theory (Gray, 1982; Gray and McNaughton, 2000), which proposes that the septo-hippocampal system is involved in inhibitory association formation and regulating the weight of affectively negative information. This theory suggests that the hippocampus and amygdala differentially contribute to mechanisms underlying anxiety and fear, respectively. Whilst fear, processed in the amygdala, is a phasic response to explicit, often conditioned aversive cues, anxiety, resulting from hippocampal processing, is more a tonic response to diffuse, often unconditioned aversive cues or situations. Fear may be viewed as a logical precursor to anxiety. Reciprocal connections between these two areas lend support to the suggestion that a hippocampal anxiety system provides inhibitory control over an amygdala fear system.

Functional and structural studies of the hippocampus in humans have provided evidence for an association with anxiety and other NA states, however results regarding the direction of activity change, or volume, are inconsistent across studies, possibly due to a failure in recognising hippocampal subregions, and in some cases, a failure to separate the hippocampus from nearby structures such as the amygdala. In healthy individuals, NA has been positively correlated with hippocampal activity. For example, increased hippocampal activity has been reported during viewing of negative stimuli (Lane et al., 1997). In patients with high-NA related disorders compared to controls, both increased (Sakai et al., 2005) and decreased (Juengling et al., 2003; Saxena et al., 2001) resting hippocampal activity has been reported.

Hippocampal volume reductions, although not consistent, have been reported in mood, anxiety, and some personality disorders with a high NA component (Davidson et al., 2002a; Tebartz van Elst et al., 2003). Whether this atrophy is associated with NA however, is questionable. A large body of evidence suggests that hippocampal atrophy may result from chronic and repeated excitatory damage as a result of stress induced HPA-axis dysfunction occurring over the course of illness or with recurrent episodes (Harrison, 2002), or resulting from early experiences such as childhood trauma or abuse (Vythilingam et al., 2002). Enlarged hippocampal volume might be associated with high NA, and indicate risk for the development of high NA related disorders. In one study of

healthy individuals, a positive correlation was found between hippocampal volume and trait anxiety (Rauch et al., 2003). There has been some research however, suggesting hippocampal atrophy might occur prior to the development of some high NA related disorders. Gilbertson et al. (2002), for example, provides evidence that smaller hippocampi might represent a pre-existing, familial vulnerability factor for the development of Post-Traumatic Stress Disorder (PTSD).

3.1.2. The right dorsolateral prefrontal cortex

The DLPFC is though to have a key role in working memory and goal directed behaviour. This area is thought to maintain the representation of goals and the means to achieve them (Davidson and Irwin, 1999). Davidson and colleagues (Davidson and Irwin, 1999; Davidson et al., 2002b) suggest that the right DLPFC (and other right prefrontal regions) are important components of Gray's BIS, and are specifically involved in withdrawal-related negative affective states, whilst the left DLPFC (and other left prefrontal regions) are important components of Gray's BAS, and are specifically involved in approach-related positive affective states. Based on early EEG studies showing greater relative right frontal activation to be associated with high NA states, it was proposed that right DLPFC activity is associated with NA states. It has been suggested, however, that in many of these studies, a relative right activation was likely to have resulted from reduced left activation rather than increased right activation (Coan and Allen, 2004).

More recent evidence using functional and structural MRI suggests that the right DLPFC's role in NA is more likely to be as an inhibitor of negative affects projecting from subcortical areas (Mayberg, 2003). In line with this theory, the right DLPFC has been implicated in NA in both healthy individuals and those with high NA related disorders. In healthy individuals, decreased activation of the right DLPFC has been reported during the production of negative affective states (Liotti et al., 2000; Mayberg et al., 1999). Increases in right DLPFC activation have been reported with cognitive attempts to suppress negative mood (Levesque et al., 2003) and arousal (Beauregard et al., 2001). Reduced activity and reduced volume of the right DLPFC have been robust findings in patients with mood disorders, where high NA is a feature (Drevets, 1999; Mayberg, 2003). Note that no study to date has examined the structural correlates of NA in this part of the brain in healthy individuals. Together however, these findings are suggestive of right DLPFC dysfunction being related to a deficit in the ability to suppress or inhibit NA.

3.1.3. The anterior cingulate cortex

The ACC is a medial limbic structure that plays a key role in the regulation of emotional and cognitive behaviour. There is strong evidence that the dorsal part of the ACC is related to cognition, whereas the ventral part is more related to emotion (Bush et al., 2000, 2002). A rostral region has also been identified, and is thought to act as an interface between the two regions, integrating cognitive and affective material (Yamasaki et al., 2002). The ventral division has been particularly implicated in NA. There is evidence that this division is primarily involved in assessing the salience of emotional and motivational information and the regulation of emotional responses. It has strong afferent connections with the amygdala, which probably relay negative, fear-related information. Efferent connections to autonomic, endocrine and visceral effectors likely contribute to the modulation of somatic and autonomic symptoms associated with the experience of negative affect (Blumberg et al., 2000). Early animal studies, for example, found electrical stimulation of the ventral ACC to result in increased heart rate, blood pressure and respiration, as well as increased distress vocalisations and facial expression (see Allman et al., 2001).

Induced negative mood in healthy individuals has been reported to result in increased activity in the ventral ACC (Liotti et al., 2000), and higher resting activity in the ventral ACC has been reported in individuals with higher self-reported trait NA (Zald et al., 2002). Activation of the ventral ACC has been reported in anxiety disorder patients when presented with stimuli that trigger their symptoms (Allman et al., 2001), while activation of the right ventral ACC has been found to correlate positively with depression severity in MDD patients (Drevets et al., 1997).

With regard to structure, one study found that trait anticipatory anxiety correlated positively with right ACC volume in healthy individuals (Pujol et al., 2002). Ventral and dorsal portions, however, were not distinguished. A reduction in ventral ACC volume (particularly left) seems to be a robust finding in the mood disorder literature. Reduced volume has been found in early-onset, un-medicated mood disorder patients (Botteron et al., 2002), as well as in both affected and unaffected co-twins from monozygotic twin pairs discordant for MD (Drevets et al., 1997), suggesting that this abnormality may be associated with a risk factor for the development of mood disorder.

It is likely that the relationship between the ventral ACC and NA is complicated by hemispheric differences. It has been suggested that high NA states result from a dysfunction of the left ventral ACC, resulting in a disinhibition of responses driven by the right ventral ACC (Drevets, 2001). The studies mentioned lend support to this suggestion in that NA related activations are most often right lateralised, whilst NA related volume reductions are most often left lateralised.

3.2. Positive affectivity

Compared to NA, there is a relative paucity of research addressing the functional and structural correlates of PA. There has been much research supporting a link between PA and the neurotransmitter Dopamine (DA). There is some evidence, mostly from functional brain imaging studies, to suggest that those structures receiving rich dopaminergic projections, including the amygdala, NAcc, ACC, and DLPFC, are involved in PA.

3.2.1. The amygdala

There is some evidence for an association between the amygdala and PA (see Zald, 2003, for an excellent review). Multiple studies have reported amygdala activation in response to a range of pleasant or positively valanced stimuli. Amygdala activation has been reported, for example, during exposure to positive photographs (Hamann et al., 2002), positive emotional words (Hamann and Mao, 2002), and pleasant tastes (Small et al., 2003).

Amygdala activation has also been associated with appetitive motivation and stimulus-reward learning (see Baxter and Murray, 2002). For example, amygdala activation has been reported during anticipation of pleasant taste (O'Doherty, 2004) and monetary reward (Knutson et al., 2001a,b). Drugs of abuse possess extremely high appetitive motivational value in drug dependent individuals during abstinence. In such individuals, increased activation of the amygdala has been reported during craving (i.e. desire to use drugs) and following exposure to drug-related cues (Bonson et al., 2002; Lingford-Hughes et al., 2003)

To date, there is little evidence for a relationship between amygdala structure and PA. However recently, amygdala volume was found to correlate positively with the degree of increase in sexual drive in epilepsy patients after temporal lobe resection (Baird et al., 2004), suggesting a role for the amygdala in the appraisal of sexual incentives.

Despite a number of studies supporting an association between the amygdala and PA, the greatest body of evidence is for its preferential involvement in the processing of aversive stimuli and the experience of negative affects. As mentioned with regards to NA, however, there is suggestion that the amygdala may have a more general role in the processing of novelty. There is also a suggestion that amygdala activation may be associated more with arousal and intensity than with affective valence (Zald, 2003). The 'NA bias' in the literature may in part arise due to the greater likelihood that negative stimuli are more novel than positive stimuli, or the greater frequency and ease with which negative stimuli induce arousal and strong motivational states.

Canli (2004) reports a series of functional MRI studies lending support to the suggestion that individual differences in personality traits may be key in modulating amygdala responses to affective stimuli. In one study, greater amygdala activation to pleasant pictures was associated with self-reported extraversion (related to PA) and greater activation to negative stimuli was associated with neuroticism (related to NA). In a second study involving the viewing of emotional facial expressions (happy, sad, fearful, angry, and neutral), across all participants there was significantly greater amygdala activation to fearful compared to neutral faces, but no differences between any other emotional expression. However, taking personality differences into account, there was a significant correlation between participants' extraversion scores and amygdala activation to happy faces. Clearly, more research is needed to pinpoint the exact role of the amygdala and its relationship to NA and PA.

3.2.2. The nucleus accumbens

While the role of the amygdala in PA is quite controversial, there is consistent evidence that the NAcc is fundamentally involved in PA. Although much of this evidence comes from animal studies showing an involvement of the NAcc in the modulation of both unconditioned and learned rewarding behaviours (Berridge, 2003; Cardinal et al., 2002), the available human evidence is also supportive. In human studies, activity in the NAcc has been reported during picture-induced positive affect (Sutton, 1997), exposure to positive verbal stimuli (Hamann and Mao, 2002), and during sexual arousal in men (Rauch et al., 1999). In one study examining the neural correlates of humour, degree of humour intensity was positively correlated with activation in the NAcc (Mobbs et al., 2003), while in another study, electrical stimulation of the NAcc was found to result in bouts of mania that lasted for several days (Miyawaki et al., 2000). Anticipation of increasing monetary reward has also been shown to elicit NAcc activation, and this activation has been positively correlated with self-reported happiness (Knutson et al., 2001a). Similarly, Breiter et al. (1997) demonstrated a high correlation between subjective craving and increased activity in the NAcc in cocaine users following an infusion of cocaine.

3.2.3. The anterior cingulate cortex

The ACC receives one of the richest dopaminergic innervations of any cortical area, and there is direct evidence from human studies that the dopaminergic projection to the ACC is reward-related (Allman et al., 2001). As previously mentioned, the broad function of the dorsal ACC has been described as cognitive. To elaborate, the dorsal ACC is suggested to be part of a distributed attentional network, and has been ascribed a host of functions including effortful control over behaviour, error conflict monitoring, reward-based decision making, motivation, and motor control (Allman et al., 2001; Bush et al., 2002). The latter three functions in particular place the dorsal ACC as an important structure for guiding approach behaviour and positive affect.

Functional studies have shown increased dorsal ACC activity to be associated with states of high PA. Increased activity in the dorsal ACC was found in one study to correlate with self-reported 'rush' (i.e. feeling of euphoria) in cocaine-dependent patients after cocaine infusion (Breiter et al., 1997). Increased dorsal ACC activity has also been found during sexual arousal in healthy men (Rauch et al., 1999), and in the manic state of patients with bipolar disorder (marked by heightened mood and behaviours associated with an increased motivational drive) (Blumberg et al., 2000).

Human lesion studies have shown lesions of the dorsal ACC to result in apathetic behaviour, lack of initiation, impaired response selection and movement execution (Allman et al., 2001). Decreased activity in the dorsal ACC has been reported in patients with MDD, one of the core symptoms of which is anhedonia. Similarly, decreased volume of the dorsal ACC has also been reported in schizophrenic patients with prominent negative symptoms that include anhedonia and avolition (Sigmundsson et al., 2001).

3.2.4. The left dorsolateral prefrontal cortex

In line with Davidson's theory of the association between the left prefrontal cortex and approach-related behaviours, research with healthy controls has shown activity in the left DLPFC to correlate positively with trait PA (HarmonJones and Allen, 1997). Increased metabolism in this area has also been found with the production of positive emotional states (Davidson et al., 2002a). Dysfunction of the left DLPFC appears to be a key feature of MDD, and it is suggested that such dysfunction may be related to some deficit in the ability to experience PA. In MDD, decreased activity levels in the left DLPFC have been found to be associated with increased severity of negative symptoms (Galynker et al., 1998), and have been found to normalise following successful antidepressant treatment (Davidson et al., 2002b; Mayberg et al., 1999).

3.3. Constraint

As with PA, there appears to be more research supporting a link between neurochemistry and Constraint than research addressing the structural and functional correlates of Constraint. It has been argued that the biological basis of the dimension Constraint relates to functional activity in the serotonin (5-HT) projection system, which originates in the midbrain raphae nuclei and is known to play a major role in behavioural inhibition (Depue and Collins, 1999). We will focus primarily on regions that receive rich serotonergic projections, the dorsal ACC, DLPFC, and lateral OFC. There is both functional and structural evidence for a relationship between these structures and behavioural inhibition and low-Constraint-related psychopathologies.

3.3.1. The anterior cingulate cortex

As mentioned earlier, there is evidence that the dorsal ACC is part of a neural network subserving cognitive control. As cognitive control is key to behavioural inhibition, it is suggested that the dorsal ACC is likely to be associated with the dimension Constraint. Activation of the dorsal ACC has been reported in healthy individuals during cognitive tasks that require response inhibition, such as the Stroop interference task (Drevets and Raichle, 1998), and the go/no-go task (Casey, et al., 1997b). Activation of the dorsal ACC has also been associated with measures of social awareness. In one study, for example, dorsal ACC activation correlated with a questionnaire measure of the capacity to recognise and experience emotion from another's point of view (Lane et al., 1998).

Dorsal ACC hypoactivation associated with poor performance during the interference condition of the colour Stroop task has been reported in patients with Attention-Deficit/Hyperactivity Disorder (ADHD) (Bush et al., 1999) and schizophrenia (Carter et al., 1997). It is suggested that this performance-related ACC dysfunction might underlie the core symptoms of inattention and impulsivity in ADHD, and the prominent attentional deficits observed in schizophrenia. Hypoactivation of the dorsal ACC related to poor inhibitory control during a go/no-go task has been reported in chronic cocaine users relative to controls (Kaufman et al., 2003). Similar findings of ACC hypoactivity have been observed in opiate addicts (Forman et al., 2004). These studies suggest that diminished inhibitory control and error conflict monitoring associated with ACC dysregulation may contribute to the loss of control and compulsive drug intake that is characteristic of drug-addicted subjects (see Lubman et al., 2004 for a fuller review).

With regard to structure, increased volume of the dorsal ACC has been associated with increased inhibitory control. In one study of healthy children, a significant correlation was found between the volume of the right dorsal ACC and performance on an attentional task requiring controlled processing (Casey et al., 1997a,b,c). A small number of studies have reported dorsal ACC structural abnormalities in Constraint-related psychopathologies. For example, reduced ACC volume has been reported in cocaine dependent patients compared to controls (Franklin et al., 2002).

3.3.2. The dorsolateral prefrontal cortex

The DLPFC is also thought to be a key region in the neural network subserving cognitive control, and is thus likely to be associated with the dimension Constraint.

It has been theorised that the DLPFC and dorsal ACC work closely together within this network; while the dorsal ACC is involved in evaluative processes indicating when control needs to be engaged, the DLPFC is responsible for the strategic implementation of control over one's thoughts and actions in line with specific goals or task-oriented behaviours (Botvinick et al., 2001; MacDonald et al., 2000).

Like the dorsal ACC, several functional studies have reported DLPFC activations during cognitive tasks that require response inhibition {Barber and Carter, 2005;Lavric et al., 2004; Kelly et al., 2004;Casey et al., 1997a,b,c}. In one study using the Stroop Interference task in a sample of 7–29 year olds, DLPFC brain activation associated with interference was found to increase with age in conjunction with improved behavioural performance (Schroeter et al., 2004). In another study, temperamental impulsivity (measured by the Barratt Impulsiveness Scale) was negatively correlated with activation of the right DLPFC during response inhibition (using the Go/No-Go task) (Asahi et al., 2004).

Reduced functioning of the DLPFC has been associated with cognitive deficits in patients with low-Constraint related psychopathologies. For example, reduced DLPFC activity has been associated with planning in the Tower of London Task in patients with Obsessive Compulsive Disorder (OCD) (van den Heuvel et al., 2005). Reduced activity in the right DLPFC has been reported during the IOWA Gambling Task in heavy marijuana users compared to controls (Bolla et al., 2005).

There is some evidence for an association between DLPFC structure and Constraint. Increased volume of the right DLPFC was reported in one study to correlate with better performance on response inhibition tasks in healthy children but not children with ADHD (Casey et al., 1997a). In another study, reduced volume of the right DLPFC was found both in boys with ADHD and their unaffected siblings, suggesting that this

structural abnormality might represent a familial risk factor for ADHD (Durston et al., 2004).

Interestingly, many of the studies reporting associations between the DLPFC and Constraint have implicated the right DLPFC specifically. As discussed, the right DLPFC is thought to be involved in the inhibition of negative affective states arising from subcortical and limbic centres. It has been theorised that the right DLPFC may be a key structure involved in a variety of inhibitory control processes (Asahi et al., 2004).

3.3.3. The orbitofrontal cortex

The OFC has been ascribed a prime role in multi-modal stimulus-reinforcement associative learning. It has been suggested that different sub-regions of the OFC subserve different aspects of this function (see Kringelbach and Rolls, 2004 for an excellent review of the functional neuroanatomy of the OFC). Whilst medial areas of the OFC are thought to be involved in decoding and monitoring the reward value of reinforcers, lateral areas are thought to be involved in evaluating punishers, which when detected may lead to a change in current behaviour. The lateral area of the OFC in particular has been implicated in Constraint. It is suggested that the inability to appropriately adapt behaviour when reinforcement contingencies change underlies low Constraint-related behaviours such as impulsivity and behavioural disinhibition.

In healthy individuals, activation of the lateral OFC has been associated with response inhibition during performance of cognitive interference tasks (Elliot et al., 2000; Horn et al., 2003), and during the viewing of angry faces (Blair et al., 1999). It has been suggested that angry expressions in others serve as a signal that our behaviour is socially unacceptable and must be inhibited. Patients with OFC lesions consistently show poor performance on reversal-learning and decision-making tasks, and exhibit disinhibited and socially inappropriate behaviours (Kringelbach and Rolls, 2004). Dysfunction of the OFC has been reported in several disorders where low Constraint is prominent. For example, in drug addiction, OFC dysfunction has been suggested to underlie the loss of control associated with compulsive drug administration (Volkow and Fowler, 2000).

With regard to OFC structure, volumetric abnormalities have also been noted in patients with low Constraint disorders. Reduced volume of the lateral OFC has been reported in patients with ADHD (Hesslinger et al., 2002) and those with SUDs (Franklin et al., 2002). In one study, decreased OFC volume was reported in patients with APD, and in these patients OFC volume correlated inversely with trait impulsivity/aggression scores (Dolan et al., 2002). Decreased OFC volumes have also been reported in patients with OCD (Szeszko et al., 1999), the core symptoms (i.e. obsessions and compulsions) of which may be considered to involve low Constraint. In fact, in one study, OFC volume was found to negatively correlate with obsessive-compulsive symptom severity (Kang et al., 2004).

4. A model of the neurobiology of three affective temperaments

Clearly, research on the neurobiology of fundamental dimensions of temperament is in its infancy, and much remains to be done. Nevertheless, there is converging evidence and enough commonalities in the findings to begin to model these associations. To this end, evidence has been presented for three affective temperamental dimensions (NA, PA, and Constraint) being associated with specific networks of neural structures. This evidence comes from neurobiological studies of psychopathologies that are related to these three dimensions, as well as studies of affective processing in healthy individuals. Obviously, more direct evidence is needed from studies that specifically test the relationship between these three dimensions and measures of neurobiology. To gain a rich and full picture of these relationships, it is suggested that there should be a focus on neural circuits rather than individual structures.

It has become clear that individual brain structures do not function in isolation (Friston, 2000). Any type of human neural-based functioning is likely a property of the interactions between different brain regions with specialised functions. Many of the structures suggested to be involved in the three temperamental dimensions share strong anatomical connections. It is suggested that the functioning of the connections between these structures, perhaps even more so than the functioning of the structures themselves, may underlie individual differences in these dimensions.

Alexander et al. (1990), through anatomical investigations, proposed one of the first comprehensive models to identify neural networks underlying different behavioural functions. The model describes a series of parallel frontal-subcortical circuits connecting specific frontal regions with the striatum, globus pallidus, and thalamus. More recently, other models have been proposed that focus specifically on the neural circuits likely to underlie the perception, production, experience, and regulation of affective states and behaviours (Mayberg, 2003; Mesulam, 2000; Phillips et al., 2003; Price, 1999; Tekin and Cummings, 2002; Yamasaki et al., 2002). These models are similar in that they all propose circuits linking specific regions of the prefrontal cortex to limbic and subcortical structures. Building on these models, we propose three specific neural circuits to be associated with the three affective temperamental dimensions of NA, PA, and Constraint (see Fig. 1 for a graphical representation).

We propose that a circuit linking subcortical-limbic structures including the amygdala and ventral ACC (involved in the rapid appraisal of affective material, the production of affective states, and the regulation of autonomic responses to affective stimuli), and structures in the right hemisphere including the hippocampus, dorsal ACC and DLPFC (crucial to various executive processes, and involved in the integration of cognitive processes and affective input, and the effortful rather than automatic regulation of affective states) is crucial to NA.

A similar circuit has been described by Mayberg et al. (2003, 1999) to be fundamental to NA. They suggest

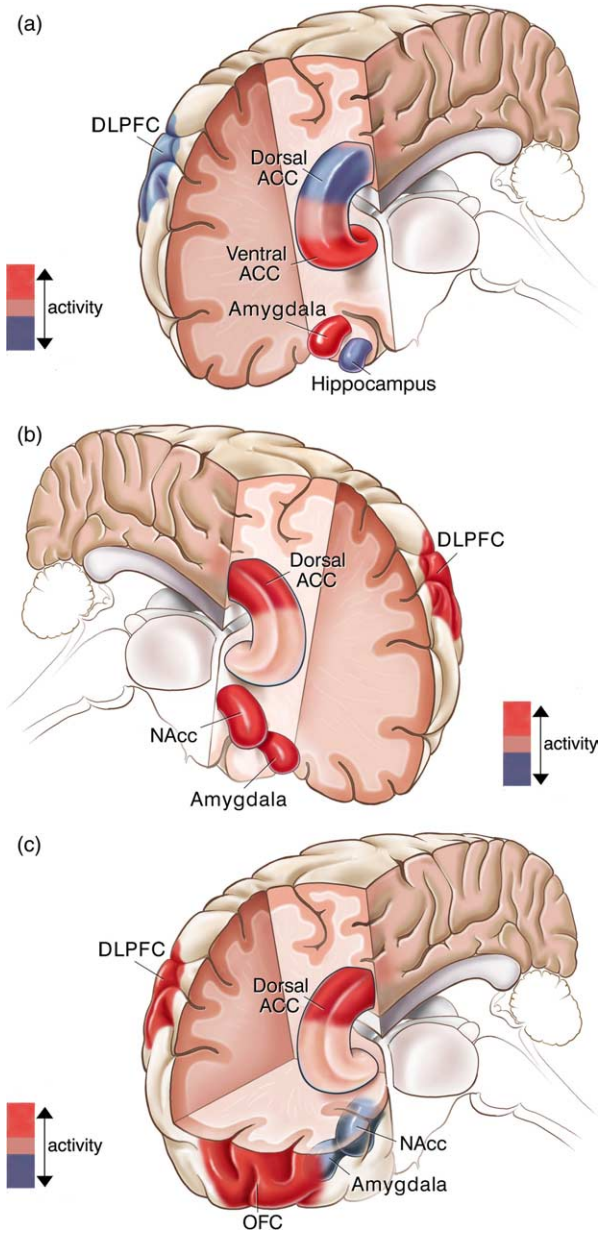

Fig. 1. Structures proposed to comprise the neural circuits underlying the three temperamental dimensions; (a) High Negative Affectivity, (b) High Positive Affectivity, (c) High Constraint. Note that the particular hemisphere chosen to display each temperament is not meant to imply that only structures in that hemisphere are implicated. However, there is evidence to suggest that the right DLPFC is particularly involved in NA, the left DLPFC is particularly involved in PA, and right prefrontal structures (DLPFC and dorsal ACC) are particularly involved in Constraint. Hipp, Hippocampus; NAcc, Nucleus Accumbens; OFC, Orbitofrontal Cortex; ACC, Anterior Cingulate Cortex; DLPFC, Dorsolateral Prefrontal Cortex.

a mutually inhibitory, reciprocal relationship between the subcortical-limbic and (particularly right) dorsal-prefrontal structures, with the rostral ACC acting as an interface between them. Based on research showing reciprocal patterns of activity in right prefrontal and subcortical-limbic structures in base-line depressed and post-treatment patients, and in transient induced sadness in both patients and controls, they propose that a lack of control or influence of right prefrontal structures over subcortical-limbic structures may explain the combination of symptoms seen in high NA states. Decreased functioning of the hippocampus, right DLPFC, and dorsal ACC might result in reduced cognitive processing skills and executive functioning, whilst consequent uncontrolled functioning of the amygdala and ventral ACC may result in abnormal somatic and autonomic responses to affective stimuli.

We propose that a similar, but left lateralised circuit linking subcortical limbic structures and dorsal prefrontal structures underlies PA, with reduced involvement of the hippocampus and ventral ACC, and the addition of the NAcc as a central component of the circuitry. The amygdala is suggested to be connected to the NAcc in a serial manner, whereby it provides the NAcc with information about the associations between discrete stimuli and reinforcements. NAcc projections to left prefrontal areas including the dorsal ACC and DLPFC are suggested to promote conscious feelings of pleasure, and influence drive to engage in pleasurable acts. In return, these prefrontal regions regulate core positive affective processing occurring in the NAcc and amygdala via downward projections.

This model is in line with recent theories of the neural circuitry underlying promotivational behaviour (Berridge, 2003; Depue and Collins, 1999). These theories stress the role of DA as a facilitator of neural processes subserving goal-directed behaviour. DA projections from the Ventral Tegmental Area (VTA) to the NAcc and prefrontal cortex are suggested to be important for PA. Supporting our model, there is evidence suggesting that DA projections may be slightly more abundant in the left hemisphere than the right.

As mentioned in the introduction, Constraint is unlikely to be an independent factor, but rather interacts with both NA and PA. The brain system underlying Constraint is therefore likely to be highly complex and involve several, if not all of the structures that have been mentioned in this review. We propose however, that the amygdala, NAcc, dorsal ACC, DLPFC, and OFC are key regions in the Constraint circuitry. The dorsal ACC, DLPFC (particularly right) and OFC (lateral sector specifically) have all been implicated in aspects of behavioural inhibition and cognitive control. It is suggested that Constraint is positively associated with the degree of inhibitory control that the dorsal ACC, DLPFC, and lateral OFC have over the amygdala and NAcc. With a reduction in this inhibitory control, behaviours may be motivated by immediate signals of reward and punishment that are encoded in the amygdala and NAcc.

Depue and Collins (1999) propose that the biological basis of Constraint is functional activity in the 5-HT projections from the midbrain raphae nuclei to motivational circuitry, including the amygdala and NAcc, and prefrontal regions involved in behavioural inhibition, including the dorsal ACC, DLPFC and OFC. Individuals with low 5-HT are hypersensitive to sensory input, such that with reward signals, behaviour is more strongly motivated by short-term than long-term goals. When faced with punishment signals, low Constraint individuals may engage in active avoidance behaviour rather than delaying action.

5. Future directions

Recent advances in imaging technology offer unique opportunities in better delineating the relationship between temperament and neurobiology. In this regard, we suggest that future studies utilise multi-modal imaging paradigms, including methods that directly assess brain connectivity, as well as incorporate other biological information such as genetics. In order to fully understand the relationship between temperament and psychopathology, prospective, longitudinal studies will be essential. These issues will be explored in more detail in the following sections.

5.1. Imaging connectivity

To identify the neural circuits underlying affective temperamental dimensions, information about the functional connectivity (i.e. the integrity of connections) between brain structures needs to be obtained. There has been speculation about the functional connectivity underlying affective functioning based mainly on findings of reciprocal activity between brain regions during affective processing, or behavioural observations following surgical disconnections in animals. There is no definitive evidence however, for the exact nature of the connections underlying affective functioning. This has largely been due to the unavailability of adequate methods. Only very recently have imaging methods been developed that allow the measurement of brain connectivity. One such method is Diffusion Tensor Imaging (DTI), a variation of MRI that measures the diffusion of water in tissues. This can help measure and quantify a tissue's orientation and structure, making it an ideal tool for examining cerebral white matter and neural fibre tracts, which provide the structural and physiological substrate of neural circuits within the central nervous system.

To date, DTI has shown promise as a tool in the assessment of white matter integrity in some psychopathologies. For example, reduced white matter integrity (thought to indicate reduced white matter connectivity) within frontal and between frontal and striatal regions has been reported in patients with schizophrenia and those with SUDs (Durston et al., 2001; Giedd et al., 1999). It is important that future research into the neurobiology of temperamental dimensions utilise measures such as DTI, in order to gain more comprehensive understanding regarding brain connectivity.

5.2. Multi-modal imaging

Most of the imaging studies reviewed have taken a unimodal imaging approach (i.e. have used either functional or structural imaging methods), and have inferred a relationship between modes. These inferences may not necessarily be valid. In neuropsychiatric research, for example, identified structural abnormalities may have no functional correlate, or conversely, functional deficits may not require a concurrent anatomic abnormality. Clearly, a combination of complimentary methodologies is necessary to better understand the nature and underlying mechanism of any identified abnormality. A multi-modal approach will be essential for the task of gaining a rich understanding of the neurobiology of temperament. Given the current emphasis on neural circuits rather than isolated brain regions, analysis of neural connectivity may be an important, if not an essential complimentary methodology.

5.3. Functional genomics

It is well accepted that variations in genetic sequences that impact gene function contribute to complex behavioural phenomena. It has been mentioned that temperament is thought to be largely genetically based. Heritability coefficients ranging from 0.2 to 0.5 have been reported in studies of the major temperamental dimensions (Rettew and McKee, 2005).

Genes also appear to be one of the most consistent risk factors identified for the development of psychopathology. While the strategy for finding susceptibility genes for disorders may be relatively straightforward, developing a useful and comprehensive understanding of the mechanisms by which such genes increase biological risk is much more of a challenge. The emerging field of functional genomics provides a promising approach to this issue. The underlying assumption of functional genomics is that functional polymorphisms in genes moderately related to behaviours and psychopathologies are more strongly related to the function of neural systems involved in processing cognitive and emotional information in the brain.

Hariri et al. (2002) for example used fMRI to explore the neural underpinnings of the relationship between an individual's genotype and brain response to emotional stimuli. They found that healthy controls with a short (compared to long) 5HTT gene promotor (*s* allele carriers) show enhanced amygdala responses to negative emotional stimuli. Since this polymorphism has also been associated with NA type characteristics (Lesch et al., 1996) as well as the development of affective illness (Lesch and Mossner, 1998), it could reflect a genetic basis for the temperamental dimension NA.

Further research by this group (Pezawas et al., 2005) has shown that *s* allele carriers have reduced grey matter volume in perigenual anterior cingulate and amygdala. Further, during processing of aversive stimuli, the same regions show strong functional interactions. In *s* allele carriers however, this circuit is relatively uncoupled, and the magnitude of cingulate-amygdala interaction is a strong predictor of temperamental anxiety. The authors state that these genotype-related alterations in structure and function of a limbic feedback circuit critical for emotion regulation possibly indicate a developmental mechanism underlying normal emotional reactivity and genetic susceptibility for affective disorder.

5.4. Prospective, longitudinal studies

The initial interest in discovering the neurobiology of temperament was largely fuelled by the quest to better understand psychopathology. Although there is much research supporting relations between temperament and

psychopathology, the factors causally responsible for these relations are not entirely clear. As mentioned, there are three basic models of the link between temperament and psychopathology: *vulnerability/pathoplasty* models, *complication/ scar* models, and *spectrum* models (Clark et al., 1994). Evidence for the *vulnerability* model is most lacking, as very few studies to date have obtained the premorbid assessment of temperament needed to test it. To test the validity of this model, prospective, longitudinal studies that track high-risk individuals are needed.

It will be important to monitor the brain development of high-risk individuals to establish whether the brain abnormalities found in individuals with diagnosed psychopathologies are present before disorder onset (i.e. represent a vulnerability or risk factor for disorder), or are a consequence of the disorder. The few studies described in the present review that have attempted to infer causality have studied remitted patients or relatively young patients, compared first to multiple-episode patients, or compared affected and unaffected monozygotic twins. Whilst useful in their own right, each of these approaches have one or more barriers to inferences of causality, such as the presence of confounding factors such as illness duration, treatment intervention, or comorbid psychopathology. Furthermore, many studies looking at young patients have failed to take into account the substantial developmental changes that are known to occur in the brain during childhood and adolescence (Giedd et al., 1999; Paus et al., 1999).

6. Conclusions

Research into (a) the neurobiology of psychopathologies involving affective disturbances, and (b) affective processes in healthy individuals, provides evidence for a relationship between three affective temperamental dimensions—NA, PA, and Constraint—and specific neural networks. These networks, in line with recent models of the neural circuitry underlying different behavioural functions, connect specific areas of the prefrontal cortex (involved in conscious behavioural and affective regulation) to subcortical-limbic structures (involved in automatic affective processing and production of affective states). NA appears to be associated with a network of regions linking the hippocampus, DLPFC (right side specifically) and dorsal ACC to limbic and subcortical regions including the ventral ACC and amygdala. PA, while receiving relatively less investigation, appears to be associated with a similar network of regions linking the DLPFC (left side specifically) and dorsal ACC to subcortical structures including the amygdala and NAcc. Constraint appears to be associated with a neural network linking the OFC, DLPFC and dorsal ACC to the NAcc and amygdala.

A comprehensive model of the neurobiological underpinnings of these core temperamental dimensions however, is far from complete. Research is required that directly tests the relationship between the dimensions and neurobiology. To develop a rich and full model, future research will need to take a multi-modal approach, combining measures of brain function, structure, chemistry and connectivity, and utilising new neuroimaging techniques such as DTI.

Given that a key motivation for examining the neurobiology of temperament is to gain a better understanding of the origins of psychopathology, it will be important for future research to utilise longitudinal, prospective designs to test the link between the neurobiology of temperament and the emergence of psychopathology. Such research will provide us with important information about the risk factors for various psychopathologies, as well as offering a clearer framework for the implementation of early intervention and neuroprotection strategies.

Acknowledgements

Dan I. Lubman is supported by the Nauma Licht Trust.

References

Adolphs, R., Damasio, A.R., 2000. Neurobiology of emotion at a systems level. In: Borod, J.C. (Ed.), The Neuropsychology of Emotion. Oxford University Press, New York, pp. 194–213.

Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, prefrontal and limbic functions. Progress in Brain Research 85, 119–146.

Allman, J.M., Hakeem, A., Erwin, J.M., Nimchinski, E., Hof, P., 2001. The anterior cingulate cortex: the evolution of an interface between emotion and cognition. Annals of the New York Academy of Sciences 935, 107–117.

Asahi, S., Okamoto, Y., Okada, G., Yamawaki, S., Yokota, N., 2004. Negative correlation between right prefrontal activity during response inhibition and impulsiveness: a fMRI study. European Archives of Psychiatry and Clinical Neuroscience 254, 245–251.

Baird, A.D., Wilson, S.J., Bladin, P.F., Saling, M.M., Reutens, D.C., 2004. The amygdala and sexual drive: insights from temporal lobe epilepsy surgery. Annals of Neurology 55, 87–96.

Bannerman, D.M., Rawlins, J.N.P., McHugh, S.B., Deacon, R.M.J., Yee, B.K., Bast, T., Zhang, W.N., Pothuizen, H.H.J., Feldon, J., 2004. Regional dissociations within the hippocampus-memory and anxiety. Neuroscience and Biobehavioral Reviews 28 (3), 273–283.

Barber, A.D., Carter, C.S., 2005. Cognitive control involved in overcoming prepotent response tendencies and switching between tasks. Cerebral Cortex 15, 899–912.

Baxter, M.G., Murray, E.A., 2002. The amygdala and reward. Nature Reviews Neuroscience 3, 563–573.

Beauregard, M., Levesque, J., Bourgouin, P., 2001. Neural correlates of conscious self-regulation of emotion. The Journal of Neuroscience 21, RC165–RC171.

Berridge, K.C., 2003. Pleasures of the brain. Brain and Cognition 52, 106–128.

Blair, R.J.R., Morris, J.S., Frith, C.D., Perrett, D.I., Dolan, R.J., 1999. Dissociable neural responses to facial expressions of sadness and anger. Brain 122, 883–893.

Blumberg, H.P., Stern, E., Martinez, D., Ricketts, S., de Asis, J., White, T., et al., 2000. Increased anterior cingulate and caudate activity in bipolar mania. Biological Psychiatry 48, 1045–1052.

Bolla, K.I., Eldreth, D.A., Matochik, J.A., Cadet, J.L., 2005. Neural substrates of faulty decision-making in abstinent marijuana users. Neuroimage 26 (2), 480–492.

Bonson, K.R., Grant, S.J., Contoreggi, C.S., 2002. Neural systems and cue-induced cocaine craving. Neuropsychopharmacology 263, 376–386.

Botteron, K.N., Raichle, M.E., Drevets, W.C., Heath, A.C., Todd, R.D., 2002. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. Biological Psychiatry 51, 342–344.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., Cohen, J.D., 2001. Conflict monitoring and cognitive control. Psychological Review 108 (3), 624–652.

Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., et al., 1997. Acute effects of cocaine on human brain activity and emotion. Neuron 19 (3), 591–611.

Bush, G., Frazier, J.A., Rauch, S.L., Seidman, L.J., Whalen, P.J., Jenike, M.A., et al., 1999. Anterior cingulate cortex dysfunction in attention-deficit/-hyperactivity disorder revealed by fMRI and the counting stroop. Biological Psychiatry 45 (12), 1542–1552.

Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences 4 (6), 215–222.

Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., et al., 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proceedings of the National Academy of Sciences of the United States of America 99 (1), 523–528.

Canli, T., 2004. Functional brain mapping of extraversion and neuroticism: learning from individual differences in emotion processing. Journal of Personality 72 (6), 1105–1132.

Cardinal, R.N., Parkinson, J.A., Hall, J., Everitt, B.J., 2002. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neuroscience and Biobehavioral Reviews 26, 321–352.

Carter, C.S., Mintun, M., Nichols, T., Cohen, J.D., 1997. Anterior cingulate Gyrus dysfunction and selective attention deficits in Schizophrenia: [15O] H_2O PET study during single-trial stroop task performance. American Journal of Psychiatry 154 (12), 1670–1675.

Casey, B.J., Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Schubert, A.B., et al., 1997a. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 36 (3), 374–383.

Casey, B.J., Trainor, R., Giedd, J., Vauss, Y., Vaituzis, C.K., Hamburger, S.D., et al., 1997b. The role of the anterior cingulate in automatic and controlled processes: a developmental neuroanatomical study. Developmental Psychobiology 30 (1), 61–69.

Casey, B.J., Trainor, R.J., Orendi, J.L., Schubert, A.B., Nystrom, L.E., Giedd, J.N., et al., 1997c. A developmental functional MRI study of prefrontal activation during performance of go-no-go task. Journal of Cognitive Neuroscience 9 (6), 835–847.

Chess, S., Thomas, A., Birch, H.G., Hertig, M., 1960. Implications of a longitudinal study of child development for child psychiatry. American Journal of Psychiatry 117, 434–441.

Clark, L.A., Watson, D., 1999. Temperament: a new paradigm for trait psychology. In: Pervin, L.A., John, O.P. (Eds.), Handbook of Personality: Theory and Research, second ed. Guilford Press, New York, pp. 399–423.

Clark, L.A., Watson, D., Mineka, S., 1994. Temperament, personality, and the mood and anxiety disorders. Journal of Abnormal Psychology 103 (1), 103–116.

Cloninger, C.R., 1986. A unified biosocial theory of personality and its role in the development of anxiety states. Psychiatry Development 3, 167–226.

Cloninger, C.R., 2000. Biology of personality dimensions. Current Opinion in Psychiatry 13 (6), 611–616.

Coan, J.A., Allen, J.J.B., 2004. Frontal EEG asymmetry as a moderator and mediator of emotion. Biological Psychiatry 67 (1–2), 7–49.

Davidson, R.J., Henriques, J., 2000. Regional brain function in sadness and depression. In: Borod, J.C. (Ed.), The Neuropsychology of Emotion. Oxford University Press, New York, pp. 269–297.

Davidson, R.J., Irwin, W., 1999. The functional neuroanatomy of emotion and affective style. Trends in Cognitive Sciences 3 (1), 11–21.

Davidson, R.J., Abercrombie, H., Nitschke, J.B., Putnam, K., 1999. Regional brain function, emotion and disorders of emotion. Current Opinion in Neurobiology 9, 228–234.

Davidson, R.J., Jackson, D.C., Kalin, N.H., 2000. Emotion, plasticity, context, and regulation: perspectives from affective neuroscience. Psychological Bulletin 126 (6), 890–909.

Davidson, R.J., Lewis, D.A., Alloy, L.B., Amaral, D.G., Bush, G., Cohen, J.D., et al., 2002a. Neural and behavioral substrates of mood and mood regulation. Biological Psychiatry 52 (6), 478–502.

Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002b. Depression: perspectives from affective neuroscience. Annual Review of Psychology 53, 545–574.

De Bellis, M.D., Casey, B.J., Dahl, R.E., Birmaher, B., Williamson, D.E., Thomas, K.M., et al., 2000. A pilot study of amygdala volumes in pediatric generalized anxiety disorder. Biological Psychiatry 48, 51–57.

Depue, R.A., Collins, P.F., 1999. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behavioral and Brain Sciences 22, 491–569.

Dolan, M.C., Deakin, J.F.W., Roberts, N., Anderson, I.M., 2002. Quantitative frontal and temporal structural MRI studies in personality-disordered offenders and control subjects. Psychiatry Research: Neuroimaging 116 (3), 133–149.

Drevets, W.C., 1999. Prefrontal cortical-amygdalar metabolism in major depression. Annals of the New York Academy of Sciences 877, 614–637.

Drevets, W.C., 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Current Opinion in Neurobiology 11, 240–249.

Drevets, W.C., Raichle, M.E., 1998. Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. Cognition and Emotion 12 (3), 353–385.

Drevets, W.C., Price, J.L., Simpson Jr., J.R., Todd, R.D., Reich, T., Vannier, M., et al., 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386 (6627), 824–827.

Durston, S., Hulshoff, P., Hilleke, E., Casey, B.J., Giedd, J.N., Buitelaar, J.K., et al., 2001. Anatomical MRI of the developing human brain: what have we learned? Journal of the American Academy of Child and Adolescent Psychiatry 40 (9), 1012–1020.

Durston, S., Pol, H.E.H., Schnack, H.G., Buitelaar, J.K., Steenhuis, M.P., Minderaa, R.B., et al., 2004. Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. Journal of the American Academy of Child and Adolescent Psychiatry 43 (3), 332–340.

Elliot, R., Dolan, R.J., Frith, C.D., 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cerebral Cortex 10, 308–317.

Eysenck, H.J., 1967. The Biological Basis of Personality. Thomas, Springfield, IL.

Forman, S.D., Dougherty, G.G., Casey, B.J., Siegle, G.J., Braver, T.S., Barch, D.M., et al., 2004. Opiate addicts lack error-dependent activation of rostral anterior cingulate. Biological Psychiatry 55 (5), 531–537.

Franklin, T.R., Acton, P.D., Maldjian, J.A., Gray, J.D., Croft, J.R., Dackis, C.A., et al., 2002. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biological Psychiatry 51, 134–142.

Friston, K.J., 2000. Experimental design and statistical issues. In: Mazziotta, J.C., Toga, A.W., Frackowiak, R.S.J. (Eds.), Brain Mapping: The Disorders. Academic Press, San Diego, CA, pp. 33–59.

Frodl, T., Meisenzahl, E.M., Zetzsche, T., Born, C., Jager, M., Groll, C., et al., 2003. Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. Biological Psychiatry 53, 338–344.

Galynker, I.I., Cai, J., Ongseng, F., Finestone, H., Dutta, E., Serseni, D., 1998. Hypofrontality and negative symptoms in major depressive disorder. Journal of Nuclear Medicine 39 (4), 608.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., et al., 1999. Brain development during childhood and adolescence: a lingitudinal MRI study. Nature Neuroscience 2 (10), 861–863.

Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., et al., 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nature Neuroscience 5 (11), 1242–1247.

Gray, J.A., 1982. The Neuropsychology of Anxiety, first ed. Oxford University Press, Oxford.

Gray, J.A., 1983. Anxiety, personality and the brain. In: Gale, H., Edwards, J.A. (Eds.), Physiological Correlates of Human Behaviour: Individual Differences and Psychopathology, vol. 3. Academic Press, New York, pp. 31–43.

Gray, J.A., 1994. Framework for a taxonomy of psychiatric disorder. In: Goozen, S.H.M.V., Poll, N.E.V.d., Sergeant, J.A. (Eds.), Emotions: Essays on Emotion Theory. Lawrence Erlbaum Associates, Hillsdale, NJ.

Gray, J.A., McNaughton, N., 2000. The Neuropsychology of Anxiety, second ed. Oxford University Press, Oxford.

Hamann, S.B., Mao, H., 2002. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. Neuroreport 13 (1), 15–19.

Hamann, S.B., Ely, T.D., Hoffman, J.M., Kilts, C.D., 2002. Ecstasy and agony: activation of the human amygdala in positive and negative emotion. Psychological Science 13 (2), 135–141.

Hariri, A.R., Mattay, V.S., Tessitore, A., 2002. Serotonin transporter genetic variation and the response of the human amygdala. Science 297, 400–403.

HarmonJones, E., Allen, J.J.B., 1997. Behavioral activation sensitivity and resting frontal EEG asymmetry: covariation of putative indicators related to risk for mood disorders. Journal of Abnormal Psychology 106 (1), 159–163.

Harrison, P.J., 2002. The neuropathology of primary mood disorder. Brain 125, 1428–1449.

Hesslinger, B., Tebartz van Elst, L., Theil, T., Haegele, K., Henning, J., Ebert, D., 2002. Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder. Neuroscience Letters 328, 319–321.

Horn, N.R., Dolan, M.C., Elliot, R., Deakin, J.F.W., Woodruff, P.W.R., 2003. Response inhibition and impulsivity: an fMRI study. Neuropsychologia 41 (14), 1959–1966.

Johnson, D.L., Wiebe, J.S., Gold, S.M., Andreasen, N.C., Hichwa, R.D., Watkins, G.L., et al., 1999. Cerebral blood flow and personality: a positron emission tomography study. American Journal of Psychiatry 156, 252–257.

Juengling, F.D., Schmahl, C., Hesslinger, B., Ebert, D., Bremner, J.D., Gostomzyk, J., et al., 2003. Positron emission tomography in female patients with Borderline personality disorder. Journal of Psychiatric Research 37 (2), 109–115.

Kagan, J., 1994. Galen's Prophecy. Basic Books, New York.

Kagan, J., 1996. Temperamental contributions to the development of social behaviour. In: Magnusson, D. (Ed.), The Lifespan Development of Individuals: Behavioural, Neurobiological and Psychosocial Perspectives. Cambridge University Press, Cambridge, pp. 377–392.

Kang, D.H., Kim, J.J., Choi, J.S., Kim, Y.I., Kim, C.W., Youn, T., et al., 2004. Volumetric investigation of the frontal-subcortical circuitry in patients with obsessive–compulsive disorder. Journal of Neuropsychiatry and Clinical Neurosciences 16 (3), 342–349.

Kaufman, J.N., Ross, T.J., Stein, E.A., Garavan, H., 2003. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. Journal of Neuroscience 23 (21), 7839–7843.

Kelly, A.M.C., Hester, R., Murphy, K., Javitt, D.C., Foxe, J.J., Garavan, H., 2004. Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI. European Journal of Neuroscience 19, 3105–3112.

Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001a. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. Journal of Neuroscience 21 (16).

Knutson, B., Momenan, R., Rawlings, R.R., Fong, G.W., Hommer, D., 2001b. Negative association of neuroticism with brain volume ratio in healthy humans. Biological Psychiatry 50, 685–690.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neurophysiology. Progress in Neurobiology 72, 341–372.

Krueger, R.F., 1999. The structure of common mental disorders. Archives of General Psychiatry 56, 921–926.

Kupfer, D.J., First, M.B., Regier, D.A. (Eds.), 2002. A Research Agenda for DSM-V. American Psychiatric Association, Washington, DC.

Lane, R.D., Reiman, E.M., Bradley, M.M., Lang, P.J., Ahern, G.L., Davidson, R.J., et al., 1997. Neuroanatomical correlates of pleasant and unpleasant emotion. Neuropsychologia 35 (11), 1437–1444.

Lane, R.D., Reiman, E.M., Axelrod, B., Yun, L., Holmes, A., Schwartz, G.E., 1998. Neural correlates of levels of emotional awareness: evidence of an interaction between emotion and attention in the anterior cingulate cortex. Journal of Cognitive Neuroscience 10 (4), 525–536.

Lavric, A., Pizzagalli, D.A., Forstmeier, S., 2004. When 'go' and 'nogo' are equally frequent: ERP components and cortical tomography. European Journal of Neuroscience 20, 2483–2488.

LeDoux, J.E., 1993. Emotional networks in the brain. In: Lewis, M., Haviland, J.M. (Eds.), Handbook of Emotions. Guilford Press, New York, pp. 109–118.

Lesch, K.P., Mossner, R., 1998. Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders? Biological Psychiatry 44, 179–192.

Lesch, K.P., Bengel, D., Heils, A., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regularatory system. Science 274, 1527–1531.

Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., et al., 2003. Neural circuitry underlying voluntary suppression of sadness. Biological Psychiatry 53 (6), 502–510.

Lingford-Hughes, A.R., Davies, S.J.C., McIver, S., Williams, T.M., Daglish, M.R.C., Nutt, D.J., 2003. Addiction. British Medical Bulletin 65, 209–222.

Liotti, M., Mayberg, H.S., Brannan, S.L., McGinnis, S., Jerabek, P., Fox, P.T., 2000. Differential limbic-cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders. Biological Psychiatry 48, 30–32.

Livesley, W.J., Jang, K.L., Vernon, P.A., 1998. Phenotypic and genetic structure of traits delineating personality disorder. Archives of General Psychiatry 55, 941–948.

Lubman, D.I., Yucel, M., Pantelis, C., 2004. Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. Addiction 99, 1491–1502.

MacDonald, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 288, 1835–1838.

Matsui, M., Gur, R.C., Turetsky, B.I., Yan, M.X.H., Gur, R.E., 2000. The relation between tendency for psychopathology and reduced frontal brain volume in healthy people. Neuropsychiatry Neuropsychology and Behavioral Neurology 13 (3), 155–162.

Mayberg, H.S., 2003. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. British Medical Bulletin 65, 193–207.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., et al., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 156 (5), 675–682.

Mesulam, M.M., 2000. Behavioral neuroanatomy: large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In: Mesulam, M.M. (Ed.), Principles of Behavioral and Cognitive Neurology, second ed. Oxford University Press, New York, pp. 1–120.

Miyawaki, E., Perlmutter, J.S., Troster, A.I., Videen, T.O., Koller, W.C., 2000. The behavioral complications of pallidal stimulation: a case report. Brain and Cognition 42 (3), 417–434.

Mobbs, D., Greicius, M.D., Abdel-Azim, E., Menon, V., Reiss, A.L., 2003. Humor modulates the mesolimbic reward centers. Neuron 40 (5), 1041–1048.

Ochsner, K.N., Schacter, D.L., 2000. A social cognitive neuroscience approach to emotion and memory. In: Borod, J.C. (Ed.), The Neuropsychology of Emotion. Oxford University Press, New York, pp. 163–193.

O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. Current Opinion in Neurobiology 14 (6), 769–776.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., et al., 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283, 1908–1911.

Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., et al., 2005. 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: a genetic susceptability mechanism for depression. Nature Neuroscience 8 (6), 828–834.

Phillips, M.L., Drevets, W.C., Rauch, S.L., Lane, R.D., 2003. Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biological Psychiatry 53.

Price, J.L., 1999. Prefrontal cortical networks related to visceral function and mood. Annals of the New York Academy of Sciences 877, 383–396.

Pujol, J., Lopez, A., Deus, J., Cardoner, N., Vallejo, J., Capdevila, A., et al., 2002. Anatomical variability of the anterior cingulate gyrus and basic dimensions of human personality. NeuroImage 15, 847–855.

Rauch, S.L., Shin, L.M., Dougherty, D.D., Alpert, N.M., Orr, S.P., Lasko, M., et al., 1999. Neural activation during sexual and competitive arousal in healthy men. Psychiatry Research 91 (1), 1–10.

Rauch, S.L., Shin, L.M., Wright, C.I., 2003. Neuroimaging studies of amygdala function in anxiety disorders. Annals of the New York Academy of Sciences 985, 389–410.

Rettew, D.C., McKee, L., 2005. Temperament and its role in developmental psychopathology. Harvard Reviews Psychiatry 13, 14–27.

Rothbart, M.K., Ellis, L.K., Rueda, M.R., Posner, M.I., 2003. Developing mechanisms of temperamental effortful control. Journal of Personality 71 (6), 1113–1143.

Saki, Y., Kumano, H., Nishikawa, M., Sakano, Y., Kaiya, H., Imabayashi, E., Ohnishi, T., Matsuda, H., Yasuda, A., Sato, A., Diksic, M., Kuboki, T., 2005. Cerebral glucose metabolism associated with a fear network in panic disorder. Neurorport 16 (9), 927–931.

Saxena, S., Brody, A.L., Ho, M.L., Alborzian, S., Ho, M.K., Maidment, K.M., et al., 2001. Cerebral metabolism in major depression and obsessive–compulsive disorder occurring separately and concurrently. Biological Psychiatry 50 (3), 159–170.

Schaefer, S.M., Jackson, D.C., Davidson, R.J., Aguirre, G.K., Kimberg, D.Y., Thompson-Schill, S.L., 2002. Modulation of amygdalar activity by the conscious regulation of negative emotion. Journal of Cognitive Neuroscience 14 (6), 913–921.

Schmahl, C.G., Vermetten, E., Elzinga, B.M., Bremner, J.D., 2003. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. Psychiatry Research: Neuroimaging 122, 193–198.

Schroeter, M.L., Zysset, S., Wahl, M., von Cramon, D.Y., 2004. Prefrontal activation due to Stroop interference increases during development—an event-related fNIRS study. NeuroImage 23, 1317–1325.

Schwartz, C.E., Snidman, N., Kagan, J., 1999. Adolescent social anxiety as an outcome of inhibited temperament in childhood. Child and Adolescent Psychiatry 38 (8), 1008–1015.

Schwartz, C.E., Wright, C.I., Shin, L.M., Kagan, J., Rauch, S.L., 2003. Inhibited and uninhibited infants 'grown-up': adult amygdalar response to novelty. Science 300 (5627), 1952–1953.

Sheline, Y.I., 2000. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. Biological Psychiatry 48, 791–800.

Sigmundsson, T., Suckling, J., Maier, M., Williams, S.C.R., Bullmore, E.T., Greenwood, K.E., et al., 2001. Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. American Journal of Psychiatry 158 (2), 234–243.

Small, D.M., Gregory, M.D., Mak, Y.E., Gitelman, D., Mesulam, M.M., Parrish, T., 2003. Dissociation of neural representation of intensity and affective valuation in human gustation. Neuron 39 (4), 701–711.

Sugiura, M., Kawashima, R., Nakagawa, M., Okada, K., Sato, T., Goto, R., et al., 2000. Correlation between human personality and neural activity in cerebral cortex. NeuroImage 11, 541–546.

Sutton, S.K., et al., 1997. Asymmetry in prefrontal glucose metabolism during appetitive and aversive emotional states: an FDG-PET study. Psychophysiology 34, S89.

Swendsen, J.D., Conway, K.P., Rounsaville, B.J., Merikangas, K.R., 2002. Are personality traits familial risk factors for substance use disorders? Results of a controlled family study. American Journal of Psychiatry 159 (10), 1760–1766.

Szeszko, P.R., Robinson, D., Alvir, J.M.J., Bilder, R.M., 1999. Orbital frontal and amygdala volume reductions in obsessive–compulsive disorder. Archives of General Psychiatry 56 (10), 913–919.

Tebartz van Elst, L., Woermann, F.G., Lemieux, L., Trimble, M.R., 1999. Amygdala enlargement in dysthymia—a volumetric study of patients with temporal lobe epilepsy. Biological Psychiatry 46, 1614–1623.

Tebartz van Elst, L., Hesslinger, B., Thiel, T., Geiger, E., Haegele, K., Lemieux, L., et al., 2003. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. Biological Psychiatry 54, 163–171.

Tekin, S., Cummings, J.L., 2002. Frontal–subcortical neuronal circuits and clinical neuropsychiatry: an update. Journal of Psychosomatic Research 53, 647–654.

Tellegen, A., 1985. Structure of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In: Tuma, A.H., Maser, J.D. (Eds.), Anxiety and the Anxiety Disorders. Erlbaum, Hillsdale, NJ, pp. 681–706.

Turner, R.M., Hudson, I.L., Butler, P.H., Joyce, P.R., 2003. Brain function and personality in normal males: a SPECT study using statistical parametric mapping. NeuroImage 19 (3), 1145–1162.

van den Heuvel, O.A., Veltman, D.J., Groenewegen, H.J., Cath, D.C., van Balkom, A., van Hartskamp, J., et al., 2005. Frontal–striatal dysfunction during planning in obsessive–compulsive disorder. Archives of General Psychiatry 62 (3), 301–310.

Volkow, N.D., Fowler, J.S., 2000. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cerebral Cortex 10 (3), 318–325.

Vythilingam, M., Heim, C., Newport, J., Miller, A.H., 2002. Childhood trauma associated with smaller hippocampal volume in women with major depression. The American Journal of Psychiatry 159 (12), 2072–2080.

Watson, D., Gamez, W., Simms, L.J., 2005. Basic dimensions of temperament and their relation to anxiety and depression: a symptom-based perspective. Journal of Research in Personality 39, 46–66.

Whalen, P.J., 1998. Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. Current Directions in Psychological Science 7 (6), 177–188.

Widiger, T.A., Verheul, R., van den Brink, W., 1999. Personality and psychopathology. In: Pervin, L.A., John, O.P. (Eds.), Handbook of Personality: Theory and Research, second ed. Guilford Press, New York, pp. 347–366.

Yamasaki, H., LaBar, K.S., McCarthy, G., 2002. Dissociable prefrontal brain systems for attention and emotion. Proceedings of the National Academy of Sciences of the United States of America 99 (17), 11447–11451.

Youn, T., Lyoo, I.K., Kim, J.J., Park, H.J., Ha, K.S., Lee, D.S., et al., 2002. Relationship between personality trait and regional cerebral glucose metabolism assessed with positron emission tomography. Biological Psychology 60 (2–3), 109–120.

Zald, D.H., 2003. The human amygdala and the emotional evaluation of sensory stimuli. Brain Research Reviews 41 (1), 88–123.

Zald, D.H., Mattson, D.L., Pardo, J.V., 2002. Brain activity in ventromedial prefrontal cortex correlates with individual differences in negative affect. Proceedings of the National Academy of Sciences of the United States of America 99 (4), 2450–2454.