



## Review

## The biological and psychological basis of neuroticism: Current status and future directions

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## ABSTRACT

Neuroticism (N) is believed to reflect a stable disposition involving specific biological and psychological mechanisms that produce its robust association with psychopathology. The nature of these mechanisms remains unclear, however. Based on an extensive review of published evidence, we argue that three interesting leads are emerging. First, N may reflect individual differences in brain circuits involved in perception of and cognitive control over negative stimuli. More specifically, reduced connectivity between the left amygdala and ACC may impair extinction of the amygdala response to anxiety-eliciting stimuli. Second, the neural evidence matches the psychological findings, which associate N with a negative bias in attention, interpretation and recall of information, increased reactivity, and ineffective coping, and is consistent with findings of decreased cardiovascular flexibility. Third, current studies suggest that HPA-axis influences mood independently of N. Strong claims on N's biological basis, however, are not yet justified due to inconsistencies and lack of replication which are in part due to methodological limitations and N's heterogeneity. We discuss potential methodological improvements and substantive directions for future research.

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## 1. Introduction

This article reviews the evidence regarding the biological and psychological basis of the high-order personality trait Neuroticism (N). Although the term has its roots in Freudian theory, modern definitions of N are purely descriptive. Currently, N is in effect a label assigned by psychologists to a major factor that consistently emerged in factor analyses of people's response to verbal descriptors of inclinations and behaviors in daily life. This is known as the lexical paradigm of personality and is based on the assumption that language encodes what is of most importance, interest, or meaning to individuals (Goldberg et al., 1990; Matthews et al., 2003; Pervin and John, 1999). Self-report measures are the most common method of measuring N (John et al., 2008; Mathews et al., 2003; Pervin and John, 1999; Widiger et al., 1984). Objective behavioral tests have not been successful and are rarely used. Measures of N consist of items referring to negative affect, including anxiety, irritability, anger, worry, frustration, self-consciousness, sensitivity to criticism, reactivity, hostility, and vulnerability (Costa and McCrae, 1992; Eysenck and Eysenck, 1975; Ormel, 1983). Hence, N is widely defined as the tendency to experience negative affect, especially when threatened, frustrated, or facing loss.

N is the single most important factor associated with many forms of psychopathology and behavioral health, in particular the common mental disorders including anxiety, depressive, and substance use disorders (see for reviews Kotov et al., 2010; Lahey, 2009). The prospective associations between N and psychopathology have prompted many in the field to consider N a robust independent predictor of psychopathology (e.g., Fanous et al., 2007; Kendler and Prescott, 2006; Khan et al., 2005; Krueger et al., 1996; Lahey, 2009; Ormel and Wohlfarth, 1991; Ormel et al., 2001; van Os et al., 2001; Vink et al., 2009). However, some authors have raised concerns about the etiological significance of the association (Claridge and Davis, 2001; Duncan-Jones et al., 1990; Ormel et al., 2004b). First, measures of N and psychopathology, in particular anxiety and depressive disorders, overlap to a large extent and may thus partially reflect the same phenotype rather than a causal relationship. Second, it is unclear to what extent the prospective studies controlled fully for earlier episodes of mental disorder and (subclinical) psychiatric symptoms present at the time of the assessment of N. This is important because N is considerably increased during episodes of (subthreshold) psychopathology, and part of this state effect may persist after full remission of the episode (Kendler et al., 1993; Ormel et al., 2004a; Rohde et al., 1994). Finally, although N has been conceptualized as a stable personality characteristic, it has been shown that test-retest correlations steadily decrease with increasing time intervals (Ormel and Rijdsdijk, 2000; Roberts and DelVecchio, 2000; Watson and Clark, 1984). Furthermore, its genetic and environmental sources overlap to a large

extent with those of the common mental disorder, suggesting that N and psychopathology may both be outcomes with overlapping etiologies (Carey and DiLalla, 1994; Fergusson and Horwood, 2001; Hettema et al., 2006; Ormel et al., 2012; van Os and Jones, 1999). Thus, for N to become etiologically informative, we must clarify its basis.

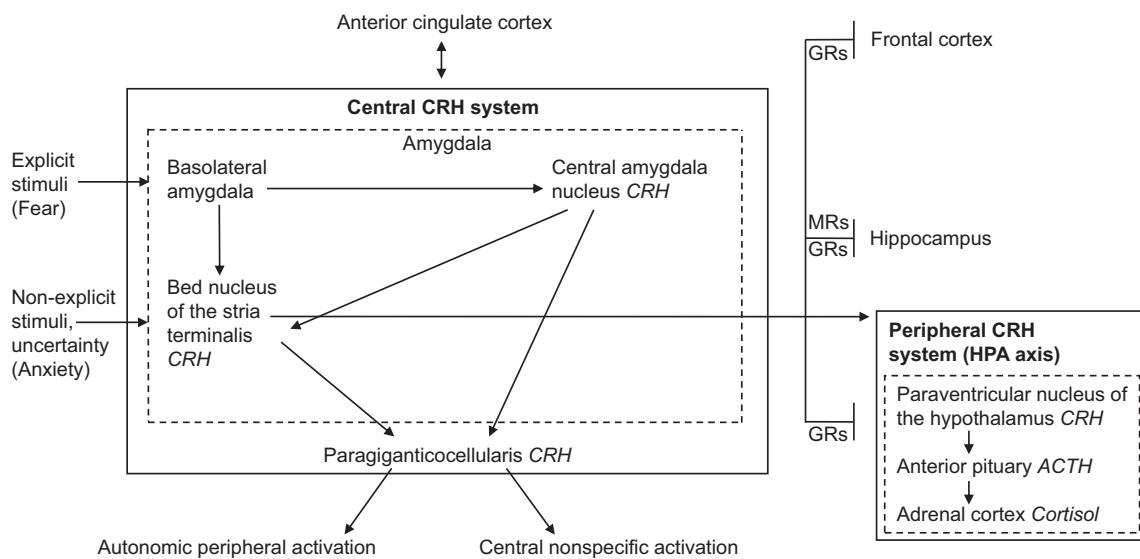
The analysis of the biological and psychological bases of N described in this paper may help to clarify the construct, elucidate its relationship with psychopathology, and support development of specific etiological hypotheses for both N and CMDs. We identified relevant studies using Web of Science and Pubmed and included human studies on correlates of N in biological domains such as the central nervous system (CNS) autonomic nervous system (ANS), and hypothalamic–pituitary–adrenal (HPA) axis, and in psychological domains such as cognition, coping, and emotional processes. We used multiple keywords for each domain in our literature search that covered the past 40 years. We not only included studies on N; but also studies on 'negative affectivity'; which is a dimension of subjective dysphoria and unpleasurable engagement (Rothbart et al., 2000; Watson and Clark, 1984). These two concepts are used interchangeably in the literature because of consensus that individuals scoring high on N measures also exhibit negative affectivity (Shankman and Klein, 2003).

## 2. The biological basis of neuroticism

### 2.1. Methodological shifts in the studies on the biological basis

Studies on the basis of N have shown a gradual but persistent shift in both research focus and methodology. 'Early' studies focused on the question whether N is linked to physiological over-responsiveness using global measures of peripheral physiological indicators and CNS arousability. Gradually, the availability of neuroimaging techniques with better spatial resolution shifted the focus to N's link with emotional reactivity and emotion regulation, by opening up the possibility of studying specific brain regions and their interactions.

The first studies were strongly inspired by Eysenck's and Gray's influential theories, which postulate that N reflects excessive physiological responsiveness (or arousability) of certain brain systems, which predisposes individuals to psychopathology (Eysenck, 1967; Eysenck and Eysenck, 1985; Gray and McNaughton, 2000). Eysenck's theory links N to lower activation thresholds in the sympathetic nervous and limbic systems. The limbic system, which consists of the hippocampus, amygdala, septum, and hypothalamus, regulates emotional states such as fear, anxiety, and aggression. Higher activation levels and lower thresholds within the limbic system would explain why high-N individuals are more easily upset in the face of minor stressors, whereas low-N people



**Fig. 1.** Schematic overview of the neurobiological systems related to neuroticism. The central corticotrophin-releasing hormone (CRH) system is composed of CRH neurons in subcortical brain regions that help mediate stress effects and emotion, memory, and central nervous system (CNS) arousal. They include CRH neurons in the central amygdala nucleus and bed nucleus of the stria terminalis (BNST), among others. Sources of CRH projections from the latter two innervate the CRH neurons in the paragiganticocellularis (PGi). The PGi, in turn, organizes autonomic peripheral activation (via the autonomic nervous system, ANS) and central nonspecific emotional activation. The peripheral system involves CRH neurons in the paraventricular nucleus (PVN) of the hypothalamus, which are activated via CRH efferents from the BNST. The PVN-CRH neurons then release CRH, which sets into motion the hypothalamic–pituitary–adrenal (HPA)-axis. The mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) play an important role in the feedback effects of cortisol. Based on "Genetic, environmental, and epigenetic factors in the development of personality disturbance" by Depue (2009). Cambridge University Press.

remain relatively unaffected under such stress. Gray's theory originally centered on trait anxiety, but in its most recent version the concept of trait anxiety resembles that of N and is linked to the sensitivity of brain systems to punishment and reward (Gray, 1991; Pickering et al., 1997). These initial studies on peripheral autonomic activation, central nonspecific activation, and the HPA axis depended largely on rather global and indirect measures of brain processes such as electrophysiological methods, skin conductance, and urinary and salivary cortisol.

Advances in brain imaging have spurred attempts to find specific neural correlates of N in the second generation of largely post-2000 research (Canli and Lesch, 2007; Cremers et al., 2010; Hariri et al., 2006). In the new millennium, researchers increasingly use techniques such as positron emission tomography (PET) and structural and functional magnetic resonance imaging (sMRI, fMRI) to investigate what N looks like in the brain. fMRI is particularly useful as its spatial resolution exceeds that of other imaging techniques and subjects can be scanned while performing cognitive tasks relevant to N and psychopathology. Coupled with advances in computing and statistics, these developments have also resulted in a stronger emphasis on emotion regulation and interaction between brain regions involved in cognitive and emotional processing. The benefits of neuroimaging do not discount the earlier research using physiological measures but neuroimaging can be seen as an important additional tool. Though still in its early stages, this research field has yielded promising findings.

## 2.2. What neural systems have been hypothesized to underlie neuroticism?

Several studies have examined N's biological manifestations in the brain. Before reviewing the evidence published over the past decades, we will briefly describe the neural systems that have been implied from a theoretical point of view. Fig. 1 shows CNS circuitry related to corticotrophin-releasing hormone (CRH) systems as an example of one of the signaling systems that has been

implicated in N. It illustrates the neural circuitry and central and peripheral systems that most studies reviewed in the next sections have sought to link to N. A basic hypothesis is that N involves an increased sensitivity of the amygdala in response to negative information (Canli, 2008; Eysenck, 1967; Gray, 1982). The amygdala interconnects with higher cortical brain regions, especially the anterior cingulate cortex (ACC) and regions in the prefrontal cortex (PFC) that are involved in the cognitive control of emotion, self-regulation, and self-referential processing. Downstream, the amygdala also integrates and coordinates behavioral, neuroendocrine, and autonomic responses to stressful stimuli by means of its connections with other brain regions such as the hypothalamus and brain stem (Depue, 2009). As illustrated in Fig. 1, the central and peripheral (CRH) systems play an important role in the mediation of the effects of stress. Both the central amygdala and structures in the bed nucleus of the stria terminalis (BNST) have outputs to hypothalamic and brain stem targets involved in emotional expression (Heimer, 2003; LeDoux, 1998). The output of the amygdala and BNST is assumed to coordinate activation of (1) the negative affective state of anxiety, which informs the individual that the current context is uncertain and potentially dangerous, (2) autonomic arousal to mobilize energy for potential action, (3) selective attention to maximize sensory input, and (4) prioritization of cognitive processes to suggest a response strategy (Depue, 2009; Jacobs et al., 2012). Studies reviewed by Depue suggest that CRH in the extended amygdala, especially the BNST, mediates prolonged anxiogenic effects and aversive contextual conditioning for as long as environmental uncertainty continues. These CRH-induced anxiogenic effects at least partly resemble the feelings and experiences to which the N-items of the facets of anxiety and stress reactivity refer. The peripheral system of the HPA axis involves CRH neurons in the paraventricular nucleus (PVN) of the hypothalamus, which are activated via CRH efferents from the BNST. The PVN-CRH neurons then release CRH, which sets into motion the HPA axis, eventually leading to secretion of cortisol.

### 3. Physiological studies

#### 3.1. Central nonspecific activation (arousability)

CNS-arousability refers to a propensity for activation of the central nervous system. Many authors have reviewed studies that indirectly examine global CNS-arousability in humans using measures of sedation threshold, electroencephalograms (EEG), or event-related potentials (ERP) (Claridge and Davis, 2001; Corr, 2004; Fahrenberg, 1992; Geen, 1997; Matthews, 1999; Stelmack, 1981; Zuckerman, 2003). These reviews show only weak and inconsistent evidence for the link between N and CNS-arousability. Studies have rarely replicated any distinct finding, but rather report many contradictory findings and complex interaction effects. For example, studies measuring sedation threshold have shown that N can be associated with both high- and low-CNS-arousability, depending on the subjects' level of extraversion (studies cited in Claridge and Davis, 2001). Similar results have been reported for subjects with different defensiveness scores (Eysenck, 2004).

Other studies have measured CNS-arousability by assessing levels of neurotransmitters, estimated from the amount of metabolites in the cerebrospinal fluid, blood, or urine. Most N studies have examined the role of serotonin and norepinephrine. Reviews of this research (Hennig, 2004; Paris, 2005; Zuckerman, 2003) have shown mixed evidence. Many correlational human studies have compared basal levels of neurotransmitters to N scores and found no relationship between N and serotonin or norepinephrine. Other studies have used challenges with drugs or mild stressors or have assessed indirect measures of transmitter response, which yielded findings that were somewhat positive, but often ambiguous or difficult to interpret. Similarly, N scores were not associated with mood change in response to direct manipulations of serotonin in the CNS (achieved through the acute depletion of its amino acid precursor tryptophan) (Booij and Van, 2007; Stewart et al., 2002). The lack of relationship is surprising given that two groups that have both been associated with elevated N scores – healthy women relative to men (Ellenbogen et al., 1996), and young adults at high risk for affective disorders (Benkelfat et al., 1994; Klaassen et al., 1999) – exhibit increased sensitivity to tryptophan depletion. Unfortunately, to date no catecholamine depletion studies have reported findings in relation to N.

In sum, there is little evidence that robust associations exist between N and the indirect measures of nonspecific CNS-arousability mentioned above. The studies published after the reviews of around the turn of the century confirm the conclusions of the reviews.

#### 3.2. Autonomic nervous system (ANS)

The ANS is another major stress regulation system of interest in the search for the physiological underpinning of N. ANS (de)regulations have been assessed by many peripheral physiological indicators such as electrodermal activity, muscle tension, pupillary response, and eye blink response, but most studies have targeted responses or levels of cardiovascular measures such as heart rate, baroreflex sensitivity (BRS) and heart rate variability (HRV). Both the sympathetic and vagal (the primary parasympathetic nerve) part of the ANS are involved in their regulation. HRV in the high frequency spectrum is thought to be an indicator for an individual's capacity to generate regulated physiological responses in the context of emotional expression with higher HRV relating to better regulation and increased flexibility (Appelhans and Luecken, 2006; Porges, 2011; Thayer et al., 2012).

The relationship between N and acute physiological responses to mental stress tasks has been studied for several decades. In their quantitative meta-analysis, Chida and Hamer (2008) reviewed

studies that were published in the last 30 years. They found that N was associated with decreased heart rate reactivity, decreased blood pressure reactivity, and poorer recovery of these cardiovascular measures after exposure to laboratory stress. However, in their meta-analysis Chida and Hamer (2008) did not find associations between N and measures of reactivity of the sympathetic ANS (e.g. pre-ejection period, skin conductance) but reported a marginally significant association between N and decreased parasympathetic reactivity (HRV). Consistent with the latter is a recent study reported higher HRV in subjects with low N during active down-regulation of negative emotion compared to passive exposure to negative stimuli, while subjects with high N reported an opposite tendency (Di Simplicio et al., 2012).

With regard to noncardial measures of ANS function, Norris et al. (2007) examined the relationship between N and skin conductance reactivity to emotionally evocative pictures. High-N individuals exhibited greater and more extended skin conductance reactivity to emotional and particularly to aversive pictures than did emotionally stable individuals. Moreover, in an adolescent sample, high N was associated with a potentiated eye blink startle reflex when participants expected an aversive stimulus in the near, but not imminent, future. Similar evidence of threat-related potentiated startle in persons with high N has been reported (Wilson et al., 2000), but another study did not detect this effect (Chan et al., 2007).

The relationship between N and basal levels of ANS activity has been less extensively studied. In particular findings of a negative relationship between N and HRV have been reported (Bleil et al., 2008; Riese et al., 2007; Watkins et al., 1998), but non replications also exist (Knyazev et al., 2002; Vassend and Knardahl, 2005). In a recent illustrative meta-analysis, several brain areas, including the medial PFC (right pregenual cingulated and right subgenual cingulated) and left sublenticular extended amygdala/ventral stratum, were found to be associated with HRV (Thayer et al., 2012). Thayer and colleagues suggest that HRV may be useful as an indicator of these brain structures that are relevant for perceptions of threat and safety, which are both central constructs in N.

Overall, these results suggest that peripheral ANS measures may not be the primary choice when aiming to study the biological basis of (changes in) N. More consistent findings may emerge when different facets of N are taken into account. HRV may be useful as an indicator for mechanisms involved in emotion regulation and social cognition affected in high-N individuals. Neuroimaging studies – as we will describe in Section 4 – also suggest that N's core reflects reduced cognitive control over negative stimuli.

#### 3.3. The HPA axis

The HPA axis is another major peripheral stress regulation system, which has been linked to N (Pariante and Lightman, 2008). Activation of the HPA-axis is measured in particular by cortisol levels and responses but also by adrenocorticotropin hormone (ACTH) increases (Heim and Nemeroff, 2002; Holsboer, 2001; Kirschbaum and Hellhammer, 1989) have reviewed human studies on the relationship between N and HPA dysregulation (Netter, 2004; Zuckerman, 2003) and did not find robust evidence of a systematic association between the two. We aim to update this review by focusing both on levels of cortisol and on cortisol responses to either psychological stress or a physiological challenge.

While some studies examining cortisol have linked N to higher levels of cortisol (Bridges and Jones, 1968; Miller et al., 1999; Nater et al., 2010; van Eck et al., 1996a; Yoshino et al., 2005), others did not replicate this finding (Adler et al., 1997; Ferguson, 2008; Schommer et al., 1999), and some even reported a negative relationship (Ballenger et al., 1983; LeBlanc and Ducharme, 2005). The cortisol awakening response, a sharp rise and fall of cortisol levels

within the first hour following awakening, is interesting in the context of N, since its magnitude is due in part to genetic factors (Bartels et al., 2003; Riese et al., 2009; Wüst et al., 2000) and is probably related to the anticipation of the stressfulness of the upcoming day (Fries et al., 2009). A recent meta-analysis found no consistent associations between N and the cortisol awakening response (Chida and Steptoe, 2009). More recent studies confirm this conclusion since they typically found no association between N and the cortisol awakening response (Gerritsen et al., 2009; van Santen et al., 2011), with two exceptions of which one found a negative association (Pineles et al., 2012) and one a positive association (Madsen et al., 2012).

Studies investigating *reactivity* of the HPA/axis may be more promising, as many scientists consider stress reactivity to be a core facet of N (Depue, 2009). Most studies in this area have attempted to activate the stress systems by exposing participants to stressful tasks, such as public speaking or executing frustrating mental arithmetic. Although some studies found a positive relationship between N and stress-induced cortisol response (Houtman and Bakker, 1991; Roger and Najarian, 1998), more studies found reduced cortisol response in high-N individuals (Gilbert et al., 1996; Hubert and Dejongmeyer, 1992; Jezova et al., 2004; Oswald et al., 2006; Phillips et al., 2005). Most studies, however, found no association between N and cortisol response (Arnetz and Fjellner, 1986; Benjamins et al., 1996; Bohnen et al., 1991; Bossert et al., 1988; Bridges and Jones, 1968; Kirschbaum et al., 1992; Roy et al., 2001; Takahashi et al., 2005; van Eck et al., 1996a,b).

Another method of investigating HPA axis dysregulation is to assess HPA-reactivity in response to a pharmacological challenge. The dexamethasone suppression test (DST) is the most common method to assess the integrity of the negative feedback mechanism of the HPA axis. Two studies have related cortisol secretion following the Dex/CRH test to N (McCleery and Goodwin, 2001; Zobel et al., 2004). McCleery and Goodwin (2001) found reduced cortisol response in high-N individuals compared to low-N individuals, while Zobel and colleagues (McCleery and Goodwin, 2001; Zobel et al., 2004) found the reverse. McCleery's study had a larger sample size ( $n = 258$  vs.  $n = 94$ ), but their subjects were young (<25 years) and many had a history of mental disorder (particularly in the high-N group). In contrast, subjects in Zobel et al.'s study had no current or past psychopathology and represented a wider age range, which is a relevant factor as cortisol responses in the Dex/CRH test increase with age (Heuser et al., 1994). These contradictory findings suggest that the presence of psychopathology may confound the relationship between N and the response to the Dex/CRH test.

Whether indexed by levels or reactivity, there is little consistent evidence showing an association between high N and dysregulation of the HPA axis. This suggests that HPA dysregulation and imbalance (up or down) influence mood independently of N. However, the lack of robust findings may have other causes (Miller et al., 2007; Nigg, 2006; Young et al., 2004). First, variability in cortisol secretion makes the timing of sampling and number of sampled days important. One recent study in a relatively large sample that assessed saliva cortisol multiple (6) times during multiple (6) days did report a positive association between total cortisol output and N (Nater et al., 2010). Second, many confounding factors were not controlled for in the studies above, including an individual's life stress history, oral contraception and medication use, cigarette smoking, history and current psychopathology, compliance to the sampling protocol, and recent chronic stress exposure (Bouma et al., 2009; Nater et al., 2010). Third, the method of cortisol assessment could be important. Some studies found associations of N with cortisol levels in plasma, but not in urine (Bridges and Jones, 1968; Miller et al., 1999; Nater et al., 2010; van Eck et al., 1996a; Yoshino et al., 2005).

Thus, while current studies suggest that the HPA-axis functions independently of N, there are methodological issues that need to be addressed in future studies to confirm this preliminary conclusion.

## 4. Neuroimaging studies

### 4.1. Neuroimaging of CNS function

The advent of functional neuroimaging techniques that allow noninvasive measurement of brain activation with high spatial resolution has led to an explosion of studies investigating the neural basis of a whole plethora of psychological functions and psychiatric symptoms over the past decades. Surprisingly though, only a dozen of studies explicitly investigated the neural correlates of N. Notably, recent fMRI studies tend to include cognitive tasks involving emotional conflict or processing of emotional (face) stimuli, which are relevant to N and psychopathology. In general, these studies have shown that N is associated with increased activity in the amygdala and ACC (Chan et al., 2008, 2009; Haas et al., 2007; Hooker et al., 2008), but associations have also been found with the medial PFC, insula, and hippocampus (Feinstein et al., 2006; Haas et al., 2008; Hooker et al., 2008). Haas et al. (2007), for instance, found a positive association between N and activation of the amygdala and subgenual ACC during emotional conflict by comparing emotionally incongruent trials relative to emotionally congruent trials in a word-face Stroop task. Bruck et al. (2011) used an emotional prosody task (emotional information is presented in the tone of voice expressed in speech) and reported strong positive correlations between measures of N and hemodynamic responses of the right amygdala, the left postcentral gyrus as well as medial frontal structures including the right ACC. Kehoe et al., 2012 observed an increased fMRI response to emotional arousal in the right medial prefrontal cortex (mPFC) in individuals with high levels of N.

Hyperreactivity in affective brain regions could be interpreted as reflecting increased arousal by emotional conflict and negative affect in high-N individuals (Chan et al., 2008; Haas et al., 2007; Hooker et al., 2008). An alternative explanation could be that high N individuals have greater vigilance for (emotional) conflict and increased attention to negative stimuli (Haas et al., 2007). In the study by Chan et al. (2009), high-N individuals showed a linear trend for increased responses to increased fear intensities in the fusiform gyrus and middle temporal gyrus, which points to more intensive visual processing of threat-relevant face stimuli. Increased amygdala activity in high N individuals might be due the role of this structure in directing attention to the salient parts of the environment (e.g. eyes) through its connections with these high-level visual areas (Vuilleumier et al., 2004). A recent study has shown that N scores are indeed positively associated with the time spent looking at the emotionally salient eye region of faces, in particular of fearful faces (Perlman et al., 2009). More evidence for negative cognitive biases in N will be discussed in the next paragraph. Here, it is important to note that the way personality differences determine what emotionally contextual information people attend to is an important factor to take into account when studying brain activity.

Although higher N scores are generally associated with increased amygdala or ACC activity, some reports show no relationship or even reduced activity (hypoactivity) (Canli et al., 2004; Thomas et al., 2001; Wolfensberger et al., 2008). Inconsistent results may be partly due to differences in experimental design. For instance, while Canli's group found a positive association between N and amygdala/ACC activation during emotional conflict situations in a word-face Stroop task (Haas et al., 2007), they did not find this association when their focus was on the contrast between negative and neutral words (i.e. emotional salience, Canli et al., 2004).

Inconsistent results may also relate to the heterogeneity of the N construct. In the study by Haas et al. (2007), the N-amygdala/ACC association was driven by their anxious (vs. depressive) subscale of N. Based on factor analyses, DeYoung et al. (2007) suggest there are two major facets of N: volatility, which relates to emotional lability, irritability and anger; and withdrawal, which primarily relates to susceptibility to negative affect. Using scales that measure these dimensions, Cunningham et al. (2011) found that overall the characteristic increased amygdala response to negative stimuli was associated with high N-Volatility only. In contrast, N-Withdrawal was only associated with increased amygdala responses when the task instruction was to approach (vs. avoid) the stimuli. Therefore, the authors conclude that the amygdala response to the valence of objects is modulated by the individual's habitual motivational style. As withdrawal and volatility scores were strongly correlated in their sample of 21 subjects, studies are warranted that investigate their conclusions regarding facets of N in larger population-based samples.

If replicated, the results from another recent fMRI study that did use selective samples based on genetic background may have important implications. Wolfensberger et al. (2008) examined 22 concordant (7 concordant high-N pairs, 15 concordant low-N pairs) and 10 discordant monozygotic (MZ) twin pairs (Wolfensberger et al., 2008). To select the twins, investigators used a composite "N" score based on a genetic factor analysis of longitudinal survey data (4 waves over 10 years) on N, trait anxiety and depression, and somatic symptoms (de Geus et al., 2007). In an emotional faces task, investigators found robust bilateral amygdala activity (faces vs. baseline) across all groups. In MZ twin pairs discordant in N, they found increased amygdala responses in high-N twins to negatively valenced faces in comparison to their low-N counterparts. In contrast, concordant high-N twin pairs unexpectedly showed blunted amygdala reactivity to both negatively and positively valenced faces compared to concordant low-N twins. The investigators reasoned that the high N scores in discordant MZ twin pairs were most likely due to environmental influences, whereas the high scores in the concordant high-N twin pairs were most likely due to genetic influences. The authors hypothesize that the blunted amygdala response coincides with increased *baseline* amygdala activation—and may reflect a protective adaptation to a history of relatively high baseline amygdala activity. Importantly, their results imply that the inconsistencies amongst previous fMRI studies of individuals with elevated N scores or at risk for psychopathology may be due in part to differences in the mix of genetically and environmentally mediated high-risk subjects in study samples (De Raedt and Koster, 2010; Wolfensberger et al., 2008). Thus, deconstructing N and examining individual differences within high-N populations will be very important targets of future research.

#### 4.2. New directions in neuroimaging research on neuroticism

##### 4.2.1. Connectivity

Neuroimaging research is gradually moving from the investigation of localized activation in brain regions toward the examination of brain connectivity between regions within distributed networks. The connections between subcortical regions such as the amygdala and cortical regions such as (parts of) the PFC, which have previously been implicated in N, are paramount for the integration of emotion and cognition (De Raedt and Koster, 2010; Pessoa, 2008). Recent functional connectivity studies are starting to shed light on the abnormal coupling between these regions in high-N individuals (Canli, 2008; Cremers et al., 2010; Kienast et al., 2008). The most striking finding from these studies is that N and trait anxiety correlate *negatively* with functional connectivity between the *left* amygdala and ACC when processing negative

facial expressions (Cremers et al., 2010; Kienast et al., 2008). Cremers and colleagues reported that, when processing similar negatively-valenced stimuli, N correlates *positively* with functional connectivity between the *right* amygdala and medial PFC (mPFC) (Cremers et al., 2010). Although self-referential processes have been suggested to rely more strongly on a ventral region of the mPFC (Mitchell et al., 2006), meta-analyses have confirmed the involvement of the dorsomedial region reported by Cremers et al. in the evaluation of self-related stimuli (Northoff et al., 2006; van der Meer et al., 2010). Though still preliminary, the findings suggest that high N might be associated with *reduced control* over and *increased self-referential evaluation* of negatively valenced stimuli. As the right amygdala may be more involved in automatic reactions (Baas et al., 2004; Dyck et al., 2011) and physiological arousal (Gerdes et al., 2010) than the left amygdala, increased activation of the right amygdala may propagate to the right mPFC to which it is strongly connected, thereby leading to increased connectivity. Reduced control may impair the extinction of the amygdala response to anxiety, while increased self-reference may relate to high-N individuals' tendency to ruminate (Cremers et al., 2010).

##### 4.2.2. Imaging genetics

Another promising recent development is the emergence of the field of "imaging genetics", a trans disciplinary fusion of (neuro)imaging and genetics, which investigates how gene variations are reflected in the structure and function of the brain. Research in this field increasingly focuses on emotional brain systems (Aleman et al., 2008; Canli, 2008), which is of particular relevance to N research. Most N-related imaging genetics studies have focused on the serotonin transporter-linked promoter region (5-HTTLPR) gene and the processing of emotional stimuli (Canli and Lesch, 2007; Canli, 2008; Hariri et al., 2006). Transcription of the 5HTTLPR gene results in the release of serotonin transporter in the synaptic cleft where it removes serotonin. Compared to the inherited long (l) variant of 5HTTLPR, the short (s) variant reduces promoter activity and transcription. The first study that combined fMRI and molecular genetics (Hariri et al., 2002) found that carriers of s-variant displayed greater amygdala activation during the presentation of angry and fearful faces than during a non-emotional control task (i.e. visuospatial matching task). Since then, various studies have confirmed greater activity in the amygdala in response to negative versus neutral stimuli in carriers of the s-variant (Furmark et al., 2004; Hariri et al., 2005; Heinz et al., 2007), but null findings have been reported as well (Bertolino et al., 2005; Wolfensberger et al., 2008). A meta-analysis of 14 studies indicated that there is an association with a moderate effect size (accounting for up to 10% of phenotypic variance) (Munafo et al., 2008).

The relationship between genetic polymorphisms and brain activation may be equivocal due to interactions with other factors. For example, it has been suggested that levels of cognitive control on the one hand and stressful life events on the other can moderate the effects of the 5-HTTLPR polymorphism on amygdala reactivity. In a similar vein, a connectivity study by Pezawas et al. (2005) shows results for 5-HTTLPR short variant carriers that are quite similar to the results reported by Cremers et al. (2010) for high N scores. Presence of the s-short variant was associated with decreased connectivity between the amygdala and ACC, but increased connectivity between amygdala and ventromedial PFC. Two interesting competing models have been proposed to elucidate the role of variation in the 5-HTTLPR gene on amygdala reactivity (Canli and Lesch, 2007; Wolfensberger et al., 2008). The "phasic activation" model argues that high N and the s-variant of the 5-HTTLPR gene enhances amygdala reactivity to briefly presented mild aversive stimuli. In contrast, the alternative "tonic activation" model posits that the high N and the s-variant increases

baseline (resting) levels of activation during the absence of stimuli processing (Canli, 2008).

These findings and models illustrate that the links between the 5-HTTLPR gene, N, environmental influences, and amygdala reactivity are complex. Clearly, further research is needed to investigate these links and to examine the role of other genes and environmental factors in amygdala reactivity. Other gene variations, such as those in the catechol-O-methyltransferase (COMT) gene, could be studied in more detail in relation to N and emotion-related brain activation (Canli, 2008).

#### 4.3. Role of gender differences

Research in large samples has shown that levels of N are higher in women than men. This is a robust finding that is consistent across cultures (Costa et al., 2001). This is especially the case during the reproductive years, but is also visible in children and elderly (Jorm, 1987). Sex differences may also be of relevance in N-related arousal, psychophysiological, neuroimaging parameters (Davidson et al., 1996). With regard to brain function, Jausovec and Jausovec (2007) showed clear differences in EEG brain responses between men and women with high scores on N. Neo and McNaughton (2011) observed a relationship between N and frontal theta power (as measured with EEG) during aversive processing, but the relationship differed for men and women.

No functional MRI studies have as yet investigated sex differences in N. However, there is reason to expect different sex-related patterns there as well. For example, Merz et al. (2010) observed an opposite pattern of brain activation in men as compared to women during fear conditioning after cortisol administration. Using structural MRI, Blankstein et al. (2009) observed a positive correlation between N and volume of the subgenual anterior cingulate cortex in female teenagers. As these brain regions are involved in social cognition and emotional processing, the authors suggested that a neuro-maturational divergence during adolescence may account for the higher prevalence of specific chronic pains and mood disorders in females. Clearly, the issue of sex differences in N and the implications for understanding N's neurobiological basis deserve more detailed and systematic investigation.

### 5. The psychological basis of neuroticism

#### 5.1. Cognition and information processing

Many well-reviewed studies have investigated how N relates to cognitive processing of emotional rather than neutral information (Eysenck, 1992; Martin, 1985; Matthews et al., 2000; Matthews, 2004; Rusting, 1998; Williams et al., 1996). Several studies have linked N to biases in attention towards emotional information (Eysenck, 2000; Matthews, 2004; Rusting, 1998; Williams et al., 1996). Compared to low-N subjects, high-N subjects show heightened attention to negative or threatening information, as evidenced by a faster response to and a slower disengagement from negative or threatening stimuli. Individuals with high N scores also exhibit biases in interpretation by construing ambiguous words in a negative way and making inferences that maintain awareness of threat. However, not all studies observed such an attentional bias (e.g., Chan et al., 2007). Indeed, several studies show that biases in attention and interpretation may only appear under stressful conditions or after mood induction (Eysenck, 2000; Mathews and MacLeod, 1994; Rusting, 1998). N is also related to a negative bias in memory (Chan et al., 2007; Martin, 1985; Rusting, 1998). High-N individuals are more likely to recall negative or threat stimuli than neutral or positive stimuli. They also recall more negative information than low-N individuals. Importantly, these associations are usually only

found if the information relates to the self (Martin, 1985; Rusting, 1998). Sometimes this bias only appears in individuals with relatively high-N scores (Rijssdijk et al., 2008).

Other research has linked N to biases at more conscious levels of cognitive processing (Matthews, 1999; Matthews et al., 2000). For example, high-N individuals have been shown to exhibit a greater tendency toward pessimism, lower self-efficacy and self-esteem, and negative self-appraisal. There is also some evidence demonstrating that worry and rumination are linked to N (Muris et al., 2005). In addition, neurotics exhibit more meta-worry (worry about worry) and excessive monitoring of mood (Matthews et al., 2000). It should be noted, however, that, because many of the measures of higher-order cognitions overlap considerably with N inventories, this type of research is in danger of establishing tautologies.

When confronted with stress, high-N individuals tend to use more passive and ineffective forms of coping, such as wishful thinking, self-blame, escape or avoidance, and denial (Lee-Baggley et al., 2005; Watson and Hubbard, 1996). They also show more interpersonally antagonistic means of coping, such as hostile reactions, venting of negative emotions, confrontational coping, and interpersonal withdrawal (Bolger and Schilling, 1991; Suls and Martin, 2005). With regard to emotion regulation, high N people make less use of reappraisal, which is an effective strategy to reduce negative effect (Gross and John, 2003).

#### 5.2. Everyday life emotional processes

Studies on the daily life emotional responses of high-N subjects have used the ecologically valid paradigm of daily life assessments, which include experience sampling and diary methods (Jacobs et al., 2011; Suls and Martin, 2005). The core of this paradigm is that individuals report on variables of interest, typically momentary affect, event occurrence, and response, several times a day or at the end of the day. In general, these studies show that people with high N-scores report more momentary negative affect (NA) and daily problems, less momentary positive affect (PA), tend to react with stronger and prolonged negative affect when confronted with an unpleasant event, and exhibit stronger reactions to recurring negative events (Bolger and Schilling, 1991; Jacobs et al., 2011; Suls and Martin, 2005).

Although the findings from studies using the daily life paradigm are relatively robust, some inconsistencies have emerged. For instance, Jacobs and colleagues did not find an association between N and increased momentary NA and reactivity. Instead, they found correlations with NA variability and (reduced) PA (Jacobs et al., 2011). In addition, the typically modest intercorrelations between most of the components of daily life emotional responses suggest that they reflect largely independent everyday life emotional processes (Jacobs et al., 2011). It is likely that these components differ in involved genes, brain processes and environmental factors, and hence in their relationship to psychopathology. Therefore, it seems important to at least distinguish between level of affect and reactivity to events. Despite the inconsistencies, there is much evidence that high-N individuals, relative to those with low-N, manifest a high emotionally-reactive phenotype in their daily interactions, which is further aggravated by ineffective coping skills.

Research on event generation explores whether high-N subjects generate stressful life events through their behavior or the environments they select. This research indicates that high N indeed predicts event exposure. Compared to low-N individuals, high-N individuals report more daily problems, conflicts, and stressful life events (Bolger and Zuckerman, 1995; Fergusson and Horwood, 1987; Headey and Wearing, 1989; Kendler et al., 2003; Magnus et al., 1993; Ormel and Wohlfarth, 1991; Poulton and Andrews, 1992; Saudino et al., 1997; Suls and Martin, 2005; Zautra et al.,

2005). Less adequate coping styles of neurotics could be involved in the generation and experience of these stressful situations. Importantly, the relationship between N and life events was shown to be independent of the well-known relationship between N and psychopathology (van Os and Jones, 1999).

## 6. Conclusions and integration

### 6.1. Preliminary conclusions: The biological basis

Exciting findings have emerged from human brain imaging studies, heart rate variability (HRV), cognitive, and daily life studies, suggesting that N reflects individual differences in cognitive control over negative stimuli with reduced amygdala-ACC connectivity in high-N individuals. However, relatively few neuroimaging studies have been conducted to date, typically on rather small samples, often using different stimuli, task parameters, and investigated brain regions. Given these limitations, our conclusions on the biological basis of N are necessarily preliminary but nonetheless provide an excellent foundation for future studies. Overall, the knowledge on the biological basis of N is not solid yet. In particular, work on central nonspecific activation (arousability) and the HPA axis is characterized by inconsistent and null findings.

Especially noteworthy is the apparent convergence of peripheral physiological (HRV) and neurobiological studies regarding reduced emotion regulation abilities in high-N persons. Combined HRV-MRI studies on N or its subcomponents are, however, scarce (Thayer et al., 2012). Two studies that measured 24-h ambulatory wake ECG and neural time series in response to affect-valence faces via fMRI found both dysregulation of coupling between limbic areas and increased autonomic output in trait anxious adults (Mujica-Parodi et al., 2009; Tolkunov et al., 2010). Advances could be made by taking an integrative approach, combining physiological and neurobiological measures in one experimental design.

Reduced connectivity may impair the extinction of the amygdala response to anxiety-eliciting stimuli. Depue (2009) suggests that variations in connectivity of the amygdala-ACC circuits manifest neurally as amygdala hyperreactivity to stress and behaviorally as anxiety, stress reactivity, and negative emotionality. Similar proposals have been advanced for the neural basis of trait anxiety (Bishop, 2007). As indicated in Fig. 1, both central amygdala and structures in the bed nucleus of the stria terminalis (BNST) output to many hypothalamic and brain stem targets related to emotional expression (Heimer, 2003; LeDoux, 1998). Hyperactivity in these regions, in the context of reduced cognitive control, may underlie anxiety and feelings of distress, persistent sensitivity to threat, increased reactivity, storage of more negative emotional memories, and decreased extinction of anxiety elicited by environmental contexts (Depue, 2009). Clearly, further research is needed to replicate, elaborate and extend these exciting findings.

### 6.2. Preliminary conclusions: The psychological basis

The evidence for N's psychological basis reveals robust associations with a negative bias in the recall of information, especially with information concerning the self. In addition, N is related to a negative bias in attention and interpretation, although mood or stress induction seems to be required to activate these biases. Moreover, N is associated with stressful event generation and ineffective coping, increased momentary negative affect (NA), less momentary positive affect (PA), and probably with increased reactivity and affect variability. There is still limited evidence relating N to higher-order cognitions, but some positive findings have emerged. Although enormous progress has been achieved, a limitation is that the research on coping and stress generation typically uses only

self-report accounts and rarely assesses actual behavior (Funder, 2001). To continue the advance, this research requires data beyond self-report questionnaires, such as peer reports, interviews, diary and event-contingent recordings in the natural environment, and direct behavioral observation (Caspi et al., 2005; Funder, 2001). Combining nomothetic and idiographic methods may be especially productive (Elavsky et al., 2012; Molenaar and Campbell, 2009).

### 6.3. Do the biological and psychological findings match?

The evidence points to persistent hyperarousal of the amygdala, possibly because of inadequate control by the ACC and other parts of the PFC, but some reports have shown no relationship or reduced activity (Thomas et al., 2001; Wolfensberger et al., 2008). If this evidence of hyperarousal is confirmed, it would strongly suggest that impairments in emotion-regulation circuits that result in hyperactivity of the amygdala underlie both N and associated psychopathology. The processes set into motion by amygdala hyperarousal may increase threat-scanning behavior. Strategies that avoid or pre-empt threat require vigilant monitoring of the environment for physical and social threats. From this perspective, the bias in attention, interpretation and the recall of information could be adaptive cognitive strategies. The tendency of high-N persons to use ineffective coping mechanisms may be due to the immediate relief that these strategies provide. With regard to emotion regulation, one would predict from psychological research that individuals high in N would show opposite patterns to individuals with high levels of dispositional mindfulness, who have been shown to be proficient at emotion regulation, psychologically (Lutz et al., 2008), and in terms of amygdala regulation (Modinos et al., 2010). A recent study supports this prediction at a neural level (Brown et al., 2012). Replicating past research, the study found that unpleasant high arousal images elicited larger late positive event-related brain potentials (LPP) than neutral images. Second, the study found that more mindful individuals showed lower LPP responses to high arousal unpleasant images, even after controlling for trait attentional control. However, N and negative affectivity, traits contrasting with mindfulness, were associated with higher LPP responses to high arousal unpleasant images.

The collective evidence fits the cognitive-adaptive theory of personality (Matthews, 1999; Matthews, 2004), which assumes that personality traits represent individual differences in approaching life's key challenges. By this theory, N relates to preference in threat-management strategies, with high-N individuals favoring strategies that avoid or pre-empt threat. Such strategies require a low detection threshold for potential threats. In a dangerous or changing environment low detection thresholds are probably adaptive, whereas in a safe and predictable environment high thresholds are probably advantageous. Given these threshold-environment links, variation in detection thresholds in the population will optimize the group's long-term inclusive fitness (Boyce and Ellis, 2005).

This adaptive aspect of N may explain why the genes linked to high N are still present in the population gene pool. If N had only maladaptive consequences, natural selection would have gradually removed the N-linked genes. Recently, Homberg and Lesch (2011) reviewed the evidence on the negative and positive effects of serotonin transporter gene variation. They concluded that the field tends to accept that the short low-expressing variant (s-allele) is associated with emotionality or stress sensitivity, although several replication failures have been reported. See also (Canli and Lesch, 2007; Caspi et al., 2010; Hariri et al., 2006) In addition, Homberg and colleagues concluded that hypervigilance, mediated by hyperactivity in corticolimbic structures, may underlie both "anxiety-related traits and (social) cognitive superiority of s-allele carriers" and that environmental factors determine whether the outcome is positive

or negative. Thus, the reason why N-related genes are still among us, is perhaps that sensitivity to environmental influences is for better or worse, that is, that a heightened emotional reactivity to negative events co-occurs with a heightened reactivity to positive events (Belsky and Pluess, 2009; Ellis et al., 2011; Homberg and Lesch, 2011; Oldehinkel et al., 2000). To date, hardly any research has addressed the possibility that N, or a major component, reflects differential sensitivity to context, involving reactivity to both negative and positive situations, and is linked to so-called plasticity genes including the s-allele. If proven correct, this could offer highly interesting and relevant new leads in the search for the basis and origins of N. In the next section, we offer some other pointers for future research.

## 7. Suggestions for future research

Understanding the basis of N will fuel the development of insightful explanatory hypotheses of N's associations with mental and behavioral health and other outcomes. As documented above, promising insights have already been achieved. Further progress may benefit from methodological improvements and deconstruction of N, the latter to address the heterogeneity of behaviors that N-measures index. Methodological limitations include the small sample size of most studies, reliance on student and clinical samples rather than population-based samples, a lack of replicated findings, the multitude of computed correlations, and the large variation in physiological and cognitive measures. These factors increase the risk of inconsistencies and chance findings. For instance, inconsistencies can easily arise if between-study differences in sample composition involve unknown confounders, such as the proportion of individuals with high introversion (Derryberry and Reed, 1994) and childhood trauma (Heim et al., 2008).

N's heterogeneity is easiest observed at the level of the facet scales included in N measures (Pervin and John, 1999). For instance, the N trait of the California Psychological Inventory Big Five (Soto et al., 2008) distinguishes four facets (Anxiety, Irritability, Depression, and Rumination-Compulsiveness); the NEO-PI-R (Costa and McCrae, 1992) six facets (Anxiety, Angry Hostility, Depression, Self-Consciousness, Vulnerability, and Impulsiveness); the Eysenck Personality Profiler three facets (Anxiety, Inferiority, Unhappiness); the Big Five Aspects Scale (DeYoung et al., 2007) two aspects (Withdrawal, Volatility); and the Multidimensional Personality Questionnaire (MPQ) (Tellegen and Waller, 1997) three facets (Alienation, Stress Reaction, Aggression).

The most straightforward way of deconstructing N is into its lower-order core facets, an idea that has been put forth in studies on the genetic basis of personality (Jang et al., 2002), the relationship between personality and psychopathology (Livesley et al., 1998), and the neural basis of N (DeYoung et al., 2007; Cunningham et al., 2011). N may also be deconstructed in terms of everyday life emotional processes such as mean level of momentary affect versus reactivity to events (Jacobs et al., 2011; Suls and Martin, 2005). Finally, N might perhaps be deconstructed into innate versus acquired N as well, because different neurobiological substrates may underlie innate and acquired N (Wolfensberger et al., 2008).

The distinction between the core facets of inner-focused anxious distress versus outer-focused irritable distress could be especially relevant (Rothbart et al., 2000; Shiner and Caspi, 2003). Anxious distress includes tendencies toward anxiety and depression, whereas irritable distress suggests a predisposition towards frustration, irritation, hostility, and anger. This distinction between anxious and irritable distress overlaps with factor analytic findings that suggest two major components of N: withdrawal, which primarily relates to susceptibility to negative affect, and volatility, which relates to emotional lability, irritability and anger (DeYoung et al., 2007).

Multiple arguments further support deconstruction of N. First, factor analysis is central to trait definitions and measures but insensitive to causal relationships among facets. Because of this, the high-order approach negates the possibility of facet-specific underlying neurobiology. Second, evidence from the small body of facet-based research suggests that this approach may yield valuable information (Chioqueta and Stiles, 2005; Tauscher et al., 2001). Third, broadly defined N contains facets that act as general risk factors for both internalizing and externalizing symptoms (frustration/irritability) and facets that have domain-specific effects (fearfulness, shyness) (Oldehinkel et al., 2004; Ormel et al., 2005). Fourth, gene hunting and candidate gene studies may yield more replicable findings if they focus on a more homogenous deconstructed N instead of on the more heterogeneous broad domain (Schmitz et al., 2007).

When deconstructing N, it seems important to distinguish between facets, especially between reactivity to events (volatility, irritable distress) versus level of affect (anxious distress, withdrawal). It is not known how the facets and characteristics of daily life emotional processes map on each other. With regard to their functional neuroanatomy, anxious-distressed N may be mediated by reduced connectivity in a cognitive appraisal pathway involving left amygdala and ACC, whereas irritability/frustration N may be mediated by increased activation of an arousal pathway involving right amygdala and medial PFC. We further conjecture that reactivity facets are largely innate, and one of the determinants of level of affect, whereas level of affect is largely due to interactions between environmental factors and person characteristics including reactivity.

In sum, future research may benefit most from deconstruction of N, further innovative methodological and statistical improvements, integration of multidisciplinary research domains, especially neuroimaging and peripheral physiological assessments.

## 8. Concluding comments

Driven by uncertainty about the meaning of the association between N and psychopathology, we set out to review the current evidence on the biological and psychological basis of N. We felt that an insightful analysis of the basis of N would help to better understand the N construct and provide tools for theoretical advancements regarding the association between N and common mental disorders (Carey and DiLalla, 1994; Fergusson and Horwood, 2001; Hettema et al., 2006; Ormel et al., 2005; van Os and Jones, 1999). We found that the reviewed evidence suggests that N reflects reduced control over and increased self-referential evaluation of negatively valenced stimuli. Physiological and neurobiological studies seem to converge on the finding of reduced emotion regulatory abilities in high N. This might be due to reduced connectivity within an amygdala-ACC/PFC neural circuit, which in turn may impair the extinction of the amygdala response to anxiety-eliciting stimuli. Given the methodological limitations, this conclusion is necessarily preliminary and in need of replication and elaboration. In contrast to the imaging and peripheral physiological research, we found that the work on central nonspecific activation (arousability) and the HPA axis is characterized by inconsistent and null findings, suggesting no meaningful relationship with N.

The evidence regarding N's psychological basis is relatively robust and suggests that N is associated with a negative bias in attention, interpretation, and recall of information; stressful event generation; relatively ineffective coping; and probably with increased reactivity and affect variability. However, the validity of these findings would be strengthened by replication with measures beyond self-report questionnaires. These psychological findings are consistent with the neuroimaging findings and fit the hypothesis

that individual differences in emotion-regulation circuits, which result in hyperarousal/hyperactivity of the amygdala, underlie both N and associated psychopathology.

We feel that future research will benefit most from further innovative methodological and statistical improvements, integration of multidisciplinary research domains, and deconstruction of N. Multiple deconstructions are feasible, including anxious distress versus irritable distress or in characteristics of daily life emotional processes, especially level of negative affect versus reactivity to events. Especially productive is probably the integration of neuroimaging (e.g., connectivity) and ambulatory peripheral physiological assessments (e.g., HRV) and the use of designs that combine nomothetic and idiographic methods. Nomothetic methods are characterized by relatively large population-based samples and relatively few longitudinal assessments whereas idiographic designs typically perform a large number of assessments in small sample using ecologically valid measures such as experience sampling. The nomothetic study can be used to select the most interesting subjects for the ideographic study. Other important topics for further research are whether the reactivity component of N is also responsive to pleasant stimuli and related to genetic variation.

Elucidation of the major components of N and their basis will contribute to the discussion of whether troublesome high N is best treated by psychological or biological interventions. It may be difficult to reduce high N because of its substantial genetic background and long-term stability. However, N can change substantially over time and is susceptible to non-genetic influences (Caspi et al., 2005; Ormel et al., 2012; Roberts and DelVecchio, 2000). Furthermore, although unambiguous evidence is still lacking, some randomized clinical trials of depression suggest that both psychotherapy (Jorm, 1989) and particular antidepressants (Tang et al., 2009) may reduce N. Thus, we should not allow pessimism to slow empirical research into N's modifiability. Indeed, increasing our understanding of N's basis will aid the development of treatment and prevention programs that target the root causes of psychopathology rather than their manifestations in specific disorders.

## Conflict of interest

All authors report no conflict of interest.

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## References

- Adler, L., Wedekind, D., Pilz, J., Weniger, G., Huether, G., 1997. Endocrine correlates of personality traits: a comparison between emotionally stable and emotionally labile healthy young men. *Neuropsychobiology* 35, 205–210.
- Aleman, A., Swart, M., van Rijn, S., 2008. Brain imaging, genetics and emotion. *Biological Psychology* 79, 58–69.
- Appelhans, B.M., Luecken, L.J., 2006. Heart rate variability as an index of regulated emotional responding. *Review of General Psychology* 10, 229–240.
- Arnetz, B., Fjellner, B., 1986. Psychological predictors of neuroendocrine responses to mental stress. *Journal of Psychosomatic Research* 30, 297–305.
- Baas, D., Aleman, A., Kahn, R.S., 2004. Lateralization of amygdala activation: a systematic review of functional neuroimaging studies. *Brain Research Reviews* 45, 96–103.
- Ballenger, J.C., Post, R.M., Jimerson, D.C., Lake, C.R., Murphy, D., Zuckerman, M., Cronin, C., 1983. Biochemical correlates of personality traits in normals: an exploratory study. *Personality and Individual Differences* 4, 615–625.
- Bartels, M., Van den Berg, M., Sluyter, F., Boomsma, D.I., de Geus, E.J., 2003. Heritability of cortisol levels: review and simultaneous analysis of twin studies. *Psychoneuroendocrinology* 28, 121–137.
- Belsky, J., Pluess, M., 2009. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological Bulletin* 135, 885–908.
- Benjamins, C., Schuurs, A., Kooreman, T., Hoogstraten, J., 1996. Self-reported and physiologically measured dental anxiety, coping styles and personality traits. *Anxiety Stress Coping* 9, 151–162.
- Benkelfat, C., Ellenbogen, M.A., Dean, P., Palmour, R.M., Young, S.N., 1994. Mood-lowering effect of tryptophan depletion. Enhanced susceptibility in young men at genetic risk for major affective disorders. *Archives of General Psychiatry* 51, 687–697.
- Bertolino, A., Arciero, G., Rubino, V., Latorre, V., De Candia, M., Mazzola, V., Blasi, G., Caforio, G., Hariri, A., Kolachana, B., Nardini, M., Weinberger, D.R., Scarabino, T., 2005. Variation of human amygdala response during threatening stimuli as a function of 5'HTTLPR genotype and personality style. *Biological Psychiatry* 57, 1517–1525.
- Bishop, S.J., 2007. Neurocognitive mechanisms of anxiety: an integrative account. *Trends in Cognitive Sciences* 11, 307–316.
- Blankstein, U., Chen, J.Y.W., Mincic, A.M., McGrath, P.A., Davis, K.D., 2009. The complex minds of teenagers: neuroanatomy of personality differs between sexes. *Neuropsychologia* 47, 599–603.
- Bleil, M.E., Gianaros, P.J., Jennings, J.R., Flory, J.D., Manuck, S.B., 2008. Trait negative affect: Toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function. *Psychosomatic Medicine* 70, 328–337.
- Bohnen, N., Nicolson, N., Sulon, J., Jolles, J., 1991. Coping style, trait anxiety and cortisol reactivity during mental stress. *Journal of Psychosomatic Research* 35, 141–147.
- Bolger, N., Schilling, E.A., 1991. Personality and the problems of everyday life: the role of neuroticism in exposure and reactivity to daily stressors. *Journal of Personality* 59, 355–386.
- Bolger, N., Zuckerman, A., 1995. A framework for studying personality in the stress process. *Journal of Personality and Social Psychology* 69, 890–902.
- Booij, L., Van, d.D., 2007. Cognitive and serotonergic vulnerability to depression: convergent findings. *Journal of Abnormal Psychology* 116, 86–94.
- Bossert, S., Berger, M., Krieg, J.C., Schreiber, W., Junker, M., von Zerssen, D., 1988. Cortisol response to various stressful situations: relationship to personality variables and coping styles. *Neuropsychobiology* 20, 36–42.
- Bouma, E.M., Riese, H., Ormel, J., Verhulst, F.C., Oldehinkel, A.J., 2009. Adolescents' cortisol responses to awakening and social stress: effects of gender, menstrual phase and oral contraceptives. The TRAILS study. *Psychoneuroendocrinology* 34, 884–893.
- Boyce, W.T., Ellis, B.J., 2005. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology* 17, 271–301.
- Bridges, P.K., Jones, M.T., 1968. Relationship of personality and physique to plasma cortisol levels in response to anxiety. *Journal of Neurology, Neurosurgery, and Psychiatry* 31, 57–60.
- Brown, K.W., Goodman, R.J., Inzlicht, M., 2012. Dispositional mindfulness and the attenuation of neural responses to emotional stimuli. *Social Cognitive and Affective Neuroscience*, <http://dx.doi.org/10.1093/scan/nss004>
- Bruck, C., Kreifels, B., Kaza, E., Lotze, M., Wildgruber, D., 2011. Impact of personality on the cerebral processing of emotional prosody. *NeuroImage* 58, 259–268.
- Canli, T., 2008. Toward a neurogenetic theory of neuroticism. *Annals of the New York Academy of Sciences* 1129, 153–174.
- Canli, T., Amin, Z., Haas, B., Omura, K., Constable, R.T., 2004. A double dissociation between mood states and personality traits in the anterior cingulate. *Behavioral Neuroscience* 118, 897–904.
- Canli, T., Lesch, K.P., 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience* 10, 1103–1109.
- Carey, G., DiLalla, D.L., 1994. Personality and psychopathology: genetic perspectives. *Journal of Abnormal Psychology* 103, 32–43.
- Caspi, A., Roberts, B.W., Shiner, R.L., 2005. Personality development: stability and change. *Annual Review of Psychology* 56, 453–484.
- Caspi, A., Hariri, A.R., Holmes, A., Uher, R., Moffitt, T.E., 2010. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry* 167, 509–527.
- Chan, S.W.Y., Goodwin, G.M., Harmer, C.J., 2007. Highly neurotic never-depressed students have negative biases in information processing. *Psychological Medicine* 37, 1281–1291.
- Chan, S.W.Y., Harmer, C.J., Goodwin, G.M., Norbury, R., 2008. Risk for depression is associated with neural biases in emotional categorisation. *Neuropsychologia* 46, 2896–2903.
- Chan, S.W.Y., Norbury, R., Goodwin, G.M., Harmer, C.J., 2009. Risk for depression and neural responses to fearful facial expressions of emotion. *British Journal of Psychiatry* 194, 139–145.
- Chida, Y., Hamer, M., 2008. Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. *Psychological Bulletin* 134, 829–885.
- Chida, Y., Steptoe, A., 2009. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. *Biological Psychology* 80, 265–278.

- Choiqueta, A.P., Stiles, T.C., 2005. Personality traits and the development of depression, hopelessness, and suicide ideation. *Personality and Individual Differences* 38, 1283–1291.
- Claridge, G., Davis, C., 2001. What's the use of neuroticism? *Personality and Individual Differences* 31, 383–400.
- Corr, P.J., 2004. Reinforcement sensitivity theory and personality. *Neuroscience & Biobehavioral Reviews* 28, 317–332.
- Costa Jr., P.T., McCrae, R.R., 1992. Revised NEO Personality Inventory (NEO-PI-R) and the Five Factor Inventory (NEO-FFI): Professional Manual. Psychological Assessment Resources, Inc, Odessa, Florida.
- Costa, P.J., Terracciano, A., McCrae, R.R., 2001. Gender differences in personality traits across cultures: Robust and surprising findings. *Journal of Personality and Social Psychology* 81, 322–331.
- Cremers, H.R., Demenescu, L.R., Aleman, A., Renken, R., van Tol, M.J., van der Wee, N.J., Veltman, D.J., Roelofs, K., 2010. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. *Neuroimage* 49, 963–970.
- Cunningham, W.A., Arbuckle, N.L., Jahn, A., Mowrer, S.M., Abduljalil, A.M., 2011. Reprint of: Aspects of neuroticism and the amygdala: Chronic tuning from motivational styles. *Neuropsychologia* 49, 657–662.
- Davidson, K., Hall, P., MacGregor, M., 1996. Gender differences in the relation between interview-derived hostility scores and resting blood pressure. *Journal of Behavioral Medicine* 19, 185–201.
- de Geus, E.J., van't Ent, D., Wolfensberger, S.P., Heutink, P., Hoogendoijk, W.J., Boomsma, D.I., Veltman, D.J., 2007. Intrapair differences in hippocampal volume in monozygotic twins discordant for the risk for anxiety and depression. *Biological Psychiatry* 61, 1062–1071.
- De Raedt, R., Koster, E.H., 2010. Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cognitive, Affective, & Behavioral Neuroscience* 10, 50–70.
- Depue, R.A., 2009. Genetic, environmental, and epigenetic factors in the development of personality disturbance. *Development and Psychopathology* 21, 1031–1063.
- Derryberry, D., Reed, M.A., 1994. Temperament and attention: orienting toward and away from positive and negative signals. *Journal of Personality and Social Psychology* 66, 1128–1139.
- DeYoung, C.G., Quilty, L.C., Peterson, J.B., 2007. Between facets and domains: 10 aspects of the Big Five. *Journal of Personality and Social Psychology* 93, 880–896.
- Di Simplicio, M., Costoloni, G., Western, D., Hanson, B., Taggart, P., Harmer, C.J., 2012. Decreased heart rate variability during emotion regulation in subjects at risk for psychopathology. *Psychological Medicine* 42 (8), 1775–1783.
- Duncan-Jones, P., Fergusson, D.M., Ormel, J., Horwood, L.J., 1990. A model of stability and change in minor psychiatric symptoms: results from three longitudinal studies. *Psychological Medicine* 38, 1–28.
- Dyck, M., Loughead, J., Kellermann, T., Boers, F., Gur, R.C., Mathiak, K., 2011. Cognitive versus automatic mechanisms of mood induction differentially activate left and right amygdala. *Neuroimage* 54, 2503–2513.
- Elavsky, S., Molenaar, P.C.M., Gold, C.H., Williams, N.I., Aronson, K.R., 2012. Daily physical activity and menopausal hot flashes: applying a novel within-person approach to demonstrate individual differences. *Maturitas* 71, 287–293.
- Ellenbogen, M.A., Young, S.N., Dean, P., Palmour, R.M., Benkelfat, C., 1996. Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. *Neuropsychopharmacology* 15, 465–474.
- Ellis, B.J., Boyce, W.T., Belsky, J., Bakermans-Kranenburg, M., Van IJzendoorn, M.H., 2011. Differential susceptibility to the environment: an evolutionary-neurodevelopmental theory. *Development and Psychopathology* 23, 7–28.
- Eysenck, H.J., 1967. *The Biological Basis of Personality*. Charles C.Thomas, Springfield, IL.
- Eysenck, H.J., Eysenck, M.W., 1985. *Personality and Individual Differences. A Natural Science Approach*. Plenum Press, New York.
- Eysenck, H.J., Eysenck, S.B.G., 1975. *Manual of the Eysenck Personality Questionnaire. EdITS*, San Diego.
- Eysenck, M., 1992. *Anxiety: The Cognitive Perspective*. Lawrence Erlbaum Associates, Inc, Hove.
- Eysenck, M.W., 2004. Trait anxiety, repressors and cognitive biases. In: Yiend, J. (Ed.), *Cognition, Emotion and Psychopathology: Theoretical, Empirical and Clinical Directions*. Cambridge University Press, New York, pp. 49–67.
- Eysenck, M.W., 2000. A cognitive approach to trait anxiety. *European Journal of Personality* 14, 463–476.
- Fahrenberg, J., 1992. *Psychophysiology of neuroticism and emotionality*. In: Gale, A., Eysenck, M.W. (Eds.), *Individual Differences: Biological Perspectives*. Wiley, Chichester, pp. 179–227.
- Fanous, A.H., Neale, M.C., Aggen, S.H., Kendler, K.S., 2007. A longitudinal study of personality and major depression in a population-based sample of male twins. *Psychological Medicine* 37, 1163–1172.
- Feinstein, J.S., Stein, M.B., Paulus, M.P., 2006. Anterior insula reactivity during certain decisions is associated with neuroticism. *Social Cognitive and Affective Neuroscience* 1, 136–142.
- Ferguson, E., 2008. Health anxiety moderates the daytime cortisol slope. *Journal of Psychosomatic Research* 64, 487–494.
- Fergusson, D.M., Horwood, L.J., 2001. The Christchurch health and development study: review of findings on child and adolescent mental health. *Australian and New Zealand Journal of Psychiatry* 35, 287–296.
- Fergusson, D.M., Horwood, L.J., 1987. Vulnerability to life events exposure. *Psychological Medicine* 17, 739–749.
- Fries, E., Dettenborn, L., Kirschbaum, C., 2009. The cortisol awakening response (CAR): facts and future directions. *International Journal of Psychophysiology* 72, 67–73.
- Funder, D.C., 2001. Personality. *Annual Review of Psychology* 52, 197–221.
- Furmark, T., Tillfors, M., Garpenstrand, H., Marteinsdottir, I., Langstrom, B., Oreland, L., Fredrikson, M., 2004. Serotonin transporter polymorphism related to amygdala excitability and symptom severity in patients with social phobia. *Neuroscience Letters* 362, 189–192.
- Geen, R., 1997. Psychophysiological approaches to personality. In: Hogan, R., Johnson, J., Briggs, S. (Eds.), *Handbook of Personality*. Academic Press, Inc, San Diego, pp. 387–414.
- Gerdens, A.B., Wieser, M.J., Muhlberger, A., Weyers, P., Alpers, G.W., Plichta, M.M., Breuer, F., Pauli, P., 2010. Brain activations to emotional pictures are differentially associated with valence and arousal ratings. *Frontiers in Human Neuroscience* 4, 175.
- Gerritsen, L., Geerlings, M.I., Bremmer, M.A., Beekman, A.T.F., Deeg, D.J.H., Penninx, B.W.J.H., Comijs, H.C., 2009. Personality characteristics and hypothalamic-pituitary-adrenal axis regulation in older persons. *The American Journal of Geriatric Psychiatry* 17, 1077–1084.
- Gilbert, D.G., Stunkard, M.E., Jensen, R.A., Detwiler, F.R.J., Martinko, J.M., 1996. Effects of exam stress on mood, cortisol, and immune functioning: Influences of neuroticism and smoker-non-smoker status. *Personality and Individual Differences* 21, 235–246.
- Goldberg, D.P., Bridges, K.R., Cook, D., Evans, B., Grayson, D., 1990. The influence of social factors on common mental disorders destabilisation and restitution. *British Journal of Psychiatry* 156, 704–713.
- Gray, J.A., 1991. The neuropsychology of temperament. In: Strelau, J., Angleitner, A. (Eds.), *Explorations in Temperament: International Perspectives on Theory and Measurement*. Plenum, New York, pp. 105–128.
- Gray, J.A., McNaughton, N., 2000. Neural anxiety systems: relevant fault-lines to trace and treat disorders. *European Journal of Neuroscience* 12, 311.
- Gray, J.A., 1982. *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System*. Clarendon Press/Oxford University Press, New York, NY, US.
- Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology* 85, 348–362.
- Haas, B.W., Constable, R.T., Canli, T., 2008. Stop the sadness: neuroticism is associated with sustained medial prefrontal cortex response to emotional facial expressions. *Neuroimage* 42, 385–392.
- Haas, B.W., Omura, K., Constable, R.T., Canli, T., 2007. Emotional conflict and neuroticism: personality-dependent activation in the amygdala and subgenual anterior cingulate. *Behavioral Neuroscience* 121, 249–256.
- Hariri, A.R., Drabant, E.M., Munoz, K.E., Kolachana, B.S., Mattay, V.S., Egan, M.F., Weinberger, D.R., 2005. A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry* 62, 146–152.
- Hariri, A.R., Drabant, E.M., Weinberger, D.R., 2006. Imaging genetics: perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. *Biological Psychiatry* 59, 888–897.
- Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R., 2002. Serotonin transporter genetic variation and the response of the human amygdala. *Science* 297, 400–403.
- Headey, B., Wearing, A., 1989. Personality, life events, and subjective well-being: toward a dynamic equilibrium model. *Journal of Personality and Social Psychology* 57, 731–739.
- Heim, C., Nemeroff, C.B., 2002. Neurobiology of early life stress: clinical studies. *Seminars in Clinical Neuropsychiatry* 7, 147–159.
- Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology* 33, 693–710.
- Heimer, L., 2003. A new anatomical framework for neuropsychiatric disorders and drug abuse. *American Journal of Psychiatry* 160, 1726–1739.
- Heinz, A., Smolka, M.N., Braus, D.F., Wräse, J., Beck, A., Flor, H., Mann, K., Schumann, G., Buchel, C., Hariri, A.R., Weinberger, D.R., 2007. Serotonin transporter genotype (5-HTTLPR): Effects of neutral and undefined conditions on amygdala activation. *Biological Psychiatry* 61, 1011–1014.
- Hennig, J., 2004. Personality, serotonin, and noradrenaline. In: telmack, R. (Ed.), *On the Psychobiology of Personality. Essays in Honor of Marvin Zuckerman*. Elsevier Science, Oxford, pp. 389–408.
- Hettema, J.M., Neale, M.C., Myers, J.M., Prescott, C.A., Kendler, K.S., 2006. A population-based twin study of the relationship between neuroticism and internalizing disorders. *American Journal of Psychiatry* 163, 857–864.
- Heuser, I., Yassouridis, A., Holsboer, F., 1994. The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *Journal of Psychiatric Research* 28, 341–356.
- Holsboer, F., 2001. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. *Journal of Affective Disorders* 62, 77–91.
- Homberg, J.R., Lesch, K., 2011. Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry* 69, 513–519.
- Hooker, C.I., Verosky, S.C., Miyakawa, A., Knight, R.T., D'Esposito, M., 2008. The influence of personality on neural mechanisms of observational fear and reward learning. *Neuropsychologia* 46, 2709–2724.

- Houtman, I.L.D., Bakker, F.C., 1991. Individual differences in reactivity to and coping with the stress of lecturing. *Journal of Psychosomatic Research* 35, 11–24.
- Hubert, W., Dejongmeyer, R., 1992. Saliva cortisol responses to unpleasant film stimuli differ between high and low trait anxious subjects. *Neuropsychobiology* 25, 115–120.
- Jacobs, R.H.A.H., Renken, R., Aleman, A., Cornelissen, F.W., 2012. The amygdala, top-down effects, and selective attention to features. *Neuroscience and Biobehavioral reviews* 36 (9), 2069–2084, <http://dx.doi.org/10.1016/j.neubiorev.2012.05.011>.
- Jacobs, N., van Os, J., Derom, C., Thiery, E., Delespaul, P., Wichers, M., 2011. Neuroticism explained? From a non-informative vulnerability marker to informative person-context interactions in the realm of daily life. *British Journal of Clinical Psychology* 50, 19–32.
- Jang, K.L., Livesley, W.J., Angleitner, A., Riemann, R., Vernon, P.A., 2002. Genetic and environmental influences on the covariance of facets defining the domains of the five-factor model of personality. *Personality and Individual Differences* 33, 83–101.
- Jausovec, N., Jausovec, K., 2007. Personality, gender and brain oscillations. *International Journal of Psychophysiology* 66, 215–224.
- Jezova, D., Makatsori, A., Duncko, R., Moncek, F., Jakubek, M., 2004. High trait anxiety in healthy subjects is associated with low neuroendocrine activity during psychosocial stress. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 28, 1331–1336.
- John, O.P., Robins, R., Pervin, L.A., 2008. *Handbook of Personality: Theory and Research*. Guilford, New York.
- Jorm, A.F., 1989. Modifiability of trait anxiety and neuroticism – a meta-analysis of the literature. *Australian and New Zealand Journal of Psychiatry* 23, 21–29.
- Jorm, A.F., 1987. Sex differences in neuroticism: a quantitative synthesis of published research. *Australian and New Zealand Journal of Psychiatry* 21, 501–506.
- Kehoe, E.G., Toomey, J.M., Balsters, J.H., Bokde, A.L., 2012. Personality modulates the effects of emotional arousal and valence on brain activation. *Social Cognitive and Affective Neuroscience*, <http://dx.doi.org/10.1093/scan/nsr059>
- Kendler, K.S., Gardner, C.O., Prescott, C.A., 2003. Personality and the experience of environmental adversity. *Psychological Medicine* 33, 1193–1202.
- Kendler, K.S., Neale, M.C., Kessler, R.C., Heath, A.C., Eaves, L.J., 1993. A longitudinal twin study of personality and major depression in women. *Archives of General Psychiatry* 50, 853–862.
- Kendler, K.S., Prescott, C.A., 2006. *Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance use Disorders*. Guilford Press, New York.
- Khan, A.A., Jacobson, K.C., Gardner, C.O., Prescott, C.A., Kendler, K.S., 2005. Personality and comorbidity of common psychiatric disorders. *British Journal of Psychiatry* 186, 190–196.
- Kienast, T., Hariri, A.R., Schlagenauf, F., Wräse, J., Sterzer, P., Buchholz, H.G., Smolka, M.N., Grunder, G., Cumming, P., Kumakura, Y., Bartenstein, P., Dolan, R.J., Heinz, A., 2008. Dopamine in amygdala gates limbic processing of aversive stimuli in humans. *Nature Neuroscience* 11, 1381–1382.
- Kirschbaum, C., Bartussek, D., Strasburger, C.J., 1992. Cortisol responses to psychological stress and correlations with personality-trait. *Personality and Individual Differences* 13, 1353–1357.
- Kirschbaum, C., Hellhammer, D.H., 1989. Salivary cortisol in psychobiological research: an overview. *Neuropsychobiology* 22, 150–169.
- Klaassen, T., Riedel, W.J., van Someren, A., Deutz, N.E., Honig, A., van Praag, H.M., 1999. Mood effects of 24-hour tryptophan depletion in healthy first-degree relatives of patients with affective disorders. *Biological Psychiatry* 46, 489–497.
- Knyazev, G.G., Slobodskaya, H.R., Wilson, G.D., 2002. Psychophysiological correlates of behavioural inhibition and activation. *Personality and Individual Differences* 33, 647–660.
- Kotov, R., Gamez, W., Schmidt, F., Watson, D., 2010. Linking big personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychological Bulletin* 136, 768–821.
- Krueger, R.F., Caspi, A., Moffitt, T.E., Silva, P.A., McGee, R., 1996. Personality traits are differentially linked to mental disorders: a multitrait-multidiagnosis study of an adolescent birth cohort. *Journal of Abnormal Psychology* 105, 299–312.
- Lahey, B.B., 2009. Public health significance of neuroticism. *American Psychologist* 64, 241–256.
- LeBlanc, J., Ducharme, M.B., 2005. Influence of personality traits on plasma levels of cortisol and cholesterol. *Physiology & Behavior* 84, 677–680.
- LeDoux, J., 1998. *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. Simon & Schuster, New York.
- Lee-Baggley, D., Preece, M., DeLongis, A., 2005. Coping with interpersonal stress: role of big five traits. *Journal of Personality* 73, 1141–1180.
- 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.
- Lutze, A., Slagter, H.A., Dunne, J.D., Davidson, R.J., 2008. Attention regulation and monitoring in meditation. *Trends in Cognitive Sciences (Regular Edition)* 12, 163–169.
- Madsen, K.S., Jernigan, T.L., Iversen, P., Frokjaer, V.G., Mortensen, E.L., Knudsen, G.M., Baaré, W.F.C., 2012. Cortisol awakening response and negative emotionality linked to asymmetry in major limbic fibre bundle architecture. *Psychiatry Research: Neuroimaging* 201, 63–72.
- Magnus, K., Diener, E., Fujita, F., Pavot, W., 1993. Extraversion and neuroticism as predictors of objective life events: a longitudinal analysis. *Journal of Personality and Social Psychology* 65, 1046–1053.
- Martin, M., 1985. Neuroticism as cognitive predisposition toward depression: A cognitive mechanism. *Personality and Individual Differences* 6, 353–365.
- Mathews, A., Fox, E., Yiend, J., Calder, A., 2003. The face of fear: effects of eye gaze and emotion on visual attention. *Visual Cognition* 10, 823–835.
- Mathews, A., MacLeod, C., 1994. Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology* 45, 25–50.
- Matthews, G., 2004. Neuroticism from the top down: Psychophysiology and negative emotionality. In: Stelmack, R.M. (Ed.), *On the Psychobiology of Personality*. Elsevier Ltd, Oxford, pp. 249–266.
- Matthews, G., 1999. Personality and skill: a cognitive-adaptive framework. In: Ackerman, P., Kyllonen, P., Roberts, R. (Eds.), *Learning and Individual Differences: Process, Trait, and Content Determinants*. American Psychological Association, Washington, DC, pp. 251–273.
- Matthews, G., Deary, I.J., Whiteman, M.C., 2003. *Personality Traits*. Cambridge University Press, New York, NY.
- Matthews, G., Berryberry, D., Siegle, G., 2000. Personality and emotion: cognitive science perspectives. In: Hampton, S. (Ed.), *Advances in Personality Psychology*, Vol. 1. Psychology Press, Philadelphia, pp. 199–237.
- McCleery, J.M., Goodwin, G.M., 2001. High and low neuroticism predict different cortisol responses to the combined dexamethasone – CRH test. *Biological Psychiatry* 49, 410–415.
- Merz, C.J., Tabbert, K., Schreckendiek, J., Klucken, T., Vaitl, D., Stark, R., Wolf, O.T., 2010. Investigating the impact of sex and cortisol on implicit fear conditioning with fMRI. *Psychoneuroendocrinology* 35, 33–46.
- Miller, G.E., Chen, E., Zhou, E.S., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin* 133, 25–45.
- Miller, G.E., Cohen, S., Rabin, B.S., Skoner, D.P., Doyle, W.J., 1999. Personality and tonic cardiovascular, neuroendocrine, and immune parameters. *Brain, Behavior, and Immunity* 13, 109–123.
- Mitchell, J.P., Macrae, C.N., Banaji, M.R., 2006. Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron* 50, 655–663.
- Modinos, G., Ormel, J., Aleman, A., 2010. Individual differences in dispositional mindfulness and brain activity involved in reappraisal of emotion. *Social Cognitive and Affective Neuroscience* 5, 369–377.
- Molenar, P.C.M., Campbell, C.G., 2009. The new person-specific paradigm in psychology. *Current Directions in Psychological Science* 18, 112–117.
- Mujica-Parodi, L., Korgaonkar, M., Ravindranath, B., Greenberg, T., Tomasi, D., Wagshul, M., Ardekani, B., Guilfoyle, D., Khan, S., Zhong, Y., Chon, K., Malaspina, D., 2009. Limbic dysregulation is associated with lowered heart rate variability and increased trait anxiety in healthy adults. *Human Brain Mapping* 30, 47–58.
- Munafo, M.R., Brown, S.M., Hariri, A.R., 2008. Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological Psychiatry* 63, 852–857.
- Muris, P., Roelofs, J., Rassin, E., Franken, I., Mayer, B., 2005. Mediating effects of rumination and worry on the links between neuroticism, anxiety and depression. *Personality and Individual Differences* 39, 1105–1111.
- Nater, U.M., Hoppmann, C., Klumb, P.L., 2010. Neuroticism and conscientiousness are associated with cortisol diurnal profiles in adults – role of positive and negative affect. *Psychoneuroendocrinology* 35, 1573–1577.
- Neo, P.S.-, McNaughton, N., 2011. Frontal theta power linked to neuroticism and avoidance. *Cognitive, Affective & Behavioral Neuroscience* 11, 396–403.
- Netter, P., 2004. Personality and hormones. In: Stelmack, R. (Ed.), *On the Psychobiology of Personality. Essays in Honor of Marvin Zuckerman*. Elsevier Science, Oxford, pp. 353–377.
- Nigg, J.T., 2006. Temperament and developmental psychopathology. *Journal of Child Psychology and Psychiatry* 47, 395–422.
- Norris, C.J., Larsen, J.T., Cacioppo, J.T., 2007. Neuroticism is associated with larger and more prolonged electrodermal responses to emotionally evocative pictures. *Psychophysiology* 44, 823–826.
- Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., Panksepp, J., 2006. Self-referential processing in our brain – a meta-analysis of imaging studies on the self. *NeuroImage* 31, 440–457.
- Oldehinkel, A.J., Hartman, C.A., de Winter, A.F., Veenstra, R., Ormel, J., 2004. Temperament profiles associated with internalizing and externalizing problems in preadolescence. *Development and Psychopathology* 16, 421–440.
- Oldehinkel, A.J., Ormel, J., Neeleman, J., 2000. Predictors of time to remission from depression in primary care patients: do some patients benefit more from positive life change than others. *Journal of Abnormal Psychology* 109, 299–307.
- Ormel, J., 1983. Neuroticism and well-being inventories: measuring traits or states? *Psychological Medicine* 13, 165–176.
- Ormel, J., Oldehinkel, A.J., Brilman, E.I., 2001. The interplay and etiological continuity of neuroticism, difficulties and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry* 158, 885–891.
- Ormel, J., Oldehinkel, A.J., Ferdinand, R.F., Hartman, C.A., de Winter, A.F., Veenstra, R., Vollebergh, W., Minderaa, R.B., Buitelaar, J.K., Verhulst, F.C., 2005. Internalizing and externalizing problems in adolescence: general and dimension-specific effects of familial loadings and preadolescent temperament traits. *Psychological Medicine* 35, 1825–1835.
- Ormel, J., Oldehinkel, A.J., Vollebergh, W., 2004a. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Archives of General Psychiatry* 61, 990–996.

- Ormel, J., Rosmalen, J., Farmer, A., 2004b. Neuroticism: a non-informative marker of vulnerability to psychopathology. *Social Psychiatry and Psychiatric Epidemiology* 39, 906–912.
- Ormel, J., Riese, H., Rosmalen, J.G., 2012. Interpreting neuroticism scores across the adult life course: Immutable or experience-dependent set points of negative affect? *Clinical Psychology Review* 32 (1), 71–79. <http://dx.doi.org/10.1016/j.cpr.2011.10.004>.
- Ormel, J., Rijdsdijk, F.V., 2000. Continuing change in neuroticism during adulthood—structural modelling of a 16-year, 5-wave community study. *Personality and Individual Differences* 28, 461–478.
- Ormel, J., Wohlfarth, T.D., 1991. How neuroticism, long-term difficulties, and life situation change influence psychological distress: a longitudinal model. *Journal of Personality and Social Psychology* 60, 744–755.
- Oswald, L.M., Zandi, P., Nestadt, G., Potash, J.B., Kalaydjian, A.E., Wand, G.S., 2006. Relationship between cortisol responses to stress and personality. *Neuropharmacology* 31, 1583–1591.
- Pariante, C.M., Lightman, S.L., 2008. The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences* 31, 464–468.
- Paris, J., 2005. Neurobiological dimensional models of personality: a review of the models of Cloninger, Depue, and Siever. *Journal of Personality Disorders* 19, 156–170.
- Perlman, S.B., Morris, J.P., Vander Wyk, B.C., Green, S.R., Doyle, J.L., Pelphrey, K.A., 2009. Individual differences in personality predict how people look at faces. *PLoS One* 4, e5952.
- Pervin, L.A., John, O.P., 1999. *Handbook of Personality: Theory and Research*. Guilford Press, New York, NY.
- Pessoa, L., 2008. On the relationship between emotion and cognition. *Nature Reviews Neuroscience* 9, 148–158.
- Pezawas, L., Angst, J., Kasper, S., 2005. Recurrent brief depression revisited. *International Review of Psychiatry* 17, 63–70.
- Phillips, A.C., Carroll, D., Burns, V.E., Drayson, M., 2005. Neuroticism, cortisol reactivity, and antibody response to vaccination. *Psychophysiology* 42, 232–238.
- Pickering, A.D., Corr, P.J., Powell, J.H., Kumari, V., Thornton, J.C., Gray, J.A., 1997. Individual differences in reactions to reinforcing stimuli are neither black nor white: To what extent are they gray. In: Nyborg, H. (Ed.), *The Scientific Study of Human Nature: Tribute to Hans J. Eysenck at Eighty*. Pergamon/Elsevier, Amsterdam, pp. 36–67.
- Pineles, S.L., Rasmussen, A.M., Yehuda, R., Lasko, N.B., Macklin, M.L., Pitman, R.K., Orr, S.P., 2012. Predicting emotional responses to potentially traumatic events from pre-exposure waking cortisol levels: a longitudinal study of police and firefighters. *Anxiety, Stress, and Coping*. <http://dx.doi.org/10.1080/10615806.2012.672976>
- Porges, S.W., 2011. *The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-Regulation*. WW Norton & Co, New York, NY, US.
- Poulton, R.G., Andrews, G., 1992. Personality as a cause of adverse life events. *Acta Psychiatrica Scandinavica* 85, 35–38.
- Riese, H., Rosmalen, J.G., Ormel, J., van Roon, A.M., Oldehinkel, A.J., Rijdsdijk, F.V., 2007. The genetic relationship between neuroticism and autonomic function in female twins. *Psychological Medicine* 37, 257–267.
- Riese, H., Rijdsdijk, F.V., Rosmalen, J.G.M., Snieder, H., Ormel, J., 2009. Neuroticism and morning cortisol secretion: Both heritable, but no shared genetic influences. *Journal of Personality* 77, 1561–1575.
- Rijdsdijk, F.V., Riese, H., Tops, M., Snieder, H., Brouwer, W.H., Smid, H.G., Ormel, J., 2008. Neuroticism, recall bias and attention bias for valenced probes: a twin study. *Psychological Medicine*, 1–10.
- Roberts, B.W., DelVecchio, W.F., 2000. The rank-order consistency of personality traits from childhood to old age: a quantitative review of longitudinal studies. *Psychological Bulletin* 126, 3–25.
- Roger, D., Najarian, B., 1998. The relationship between emotional rumination and cortisol secretion under stress. *Personality and Individual Differences* 24, 531–538.
- Rohde, P., Lewinsohn, P.M., Seeley, J.R., 1994. Are adolescents changed by an episode of major depression? *Journal of the American Academy of Child & Adolescent Psychiatry* 33, 1289–1298.
- Rothbart, M.K., Ahadi, S.A., Evans, D.E., 2000. Temperament and personality: origins and outcomes. *Journal of Personality and Social Psychology* 78, 122–135.
- Roy, M.P., Kirschbaum, C., Steptoe, A., 2001. Psychological, cardiovascular, and metabolic correlates of individual differences in cortisol stress recovery in young men. *Psychoneuroendocrinology* 26, 375–391.
- Rusting, C.L., 1998. Personality, mood, and cognitive processing of emotional information: three conceptual frameworks. *Psychological Bulletin* 124, 165–196.
- Saudino, K.J., Pedersen, N.L., Lichtenstein, P., McClearn, G.E., Plomin, R., 1997. Can personality explain genetic influences on life events. *Journal of Personality and Social Psychology* 72, 196–206.
- Schmitz, A., Hennig, J., Kuepper, Y., Reuter, M., 2007. The association between neuroticism and the serotonin transporter polymorphism depends on structural differences between personality measures. *Personality and Individual Differences* 42, 789–799.
- Schommer, N.C., Kudielka, B.M., Hellhammer, D.H., Kirschbaum, C., 1999. No evidence for a close relationship between personality traits and circadian cortisol rhythm or a single cortisol stress response. *Psychological Reports* 84, 840–842.
- Shankman, S.A., Klein, D.N., 2003. The relation between depression and anxiety: an evaluation of the tripartite, approach-withdrawal and valence-arousal models. *Clinical Psychology Review* 23, 605–637.
- Shiner, R., Caspi, A., 2003. Personality differences in childhood and adolescence: measurement, development, and consequences. *Journal of Child Psychology and Psychiatry* 44, 2–32.
- Soto, C.J., John, O.P., Gosling, S.D., Potter, J., 2008. The developmental psychometrics of big five self-reports: acquiescence, factor structure, coherence, and differentiation from ages 10 to 20. *Journal of Personality and Social Psychology* 94, 718–737.
- Stelmack, R., 1981. The psychophysiology of extraversion and neuroticism. In: Eysenck, H. (Ed.), *A Model for Personality*. Springer, New York, pp. 38–60.
- Stewart, M., Deary, I., Ebmeier, K., 2002. Neuroticism as a predictor of mood change: the effects of tryptophan depletion. *British Journal of Psychiatry* 181, 242–247.
- Suls, J., Martin, R., 2005. The daily life of the garden-variety neurotic: reactivity, stressor exposure, mood spillover, and maladaptive coping. *Journal of Personality* 73, 1485–1509.
- Takahashi, T., Ikeda, K., Ishikawa, M., Kitamura, N., Tsukasaki, T., Nakama, D., Kameda, T., 2005. Anxiety, reactivity, and social stress-induced cortisol elevation in humans. *Neuro Endocrinology Letters* 26, 351–354.
- Tang, T.Z., DeRubeis, R.J., Hollon, S.D., Amsterdam, J., Shelton, R., Schalet, B., 2009. Personality change during depression treatment: a placebo-controlled trial. *Archives of General Psychiatry* 66, 1322–1330.
- Tauscher, J., Bagby, R.M., Javanmard, M., Christensen, B.K., Kasper, S., Kapur, S., 2001. Inverse relationship between serotonin 5-HT(1A) receptor binding and anxiety: a [(11)C]WAY-100635 PET investigation in healthy volunteers. *American Journal of Psychiatry* 158, 1326–1328.
- Tellegen, A., Waller, N.G., 1997. Exploring personality through test construction: development of the multidimensional personality questionnaire. In: Briggs, S., Cheek, J. (Eds.), *Personality Measures: Development and Evaluation*, vol. 1. JAI Press, Greenwich, CT, pp. 171–248.
- Thayer, J.F., Ahs, F., Fredrikson, M., Sollers II, J.J.I., Wager, T.D., 2012. A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience & Biobehavioral Reviews* 36, 747–756.
- Thomas, K.M., Drevets, W.C., Dahl, R.E., Ryan, N.D., Birmaher, B., Eccard, C.H., Axelson, D., Whalen, P.J., Casey, B.J., 2001. Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry* 58, 1057–1063.
- Tolkunov, D., Rubin, D., Mujica-Parodi, L., 2010. Power spectrum scale invariance quantifies limbic dysregulation in trait anxious adults using fMRI: Adapting methods optimized for characterizing autonomic dysregulation to neural dynamic time series. *Neuroimage* 50, 72–80.
- van der Meer, L., Costafreda, S., Aleman, A., David, A.S., 2010. Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neuroscience & Biobehavioral Reviews* 34, 935–946.
- van Eck, M., Berkhof, H., Nicolson, N., Sulon, J., 1996a. The effects of perceived stress, traits, mood states, and stressful daily events on salivary cortisol. *Psychosomatic Medicine* 58, 447–458.
- van Eck, M.M.M., Nicolson, N.A., Berkhof, H., Sulon, J., 1996b. Individual differences in cortisol responses to a laboratory speech task and their relationship to responses to stressful daily events. *Biological Psychology* 43, 69–84.
- van Os, J., Jones, P.B., 1999. Early risk factors and adult person-environment relationships in affective disorder. *Psychological Medicine* 29, 1055–1067.
- van Os, J., Park, S.B., Jones, P.B., 2001. Neuroticism, life events and mental health: evidence for person-environment correlation. *British Journal of Psychiatry* 178, 72–77.
- van Santen, A., Vreeburg, S.A., Van, d.D., Spinthoven, P., Zitman, F.G., Penninx, B.W.J.H., 2011. Psychological traits and the cortisol awakening response: results from the Netherlands study of depression and anxiety. *Psychoneuroendocrinology* 36, 240–248.
- Vassend, O., Knardahl, S., 2005. Personality, affective response, and facial blood flow during brief cognitive tasks. *International Journal of Psychophysiology* 55, 265–278.
- Vink, D., Aartsen, M.J., Comijs, H.C., Heymans, M.W., Penninx, B.W.J.H., Stek, M.L., Deeg, D.J.H., Beekman, A.T.F., 2009. Onset of anxiety and depression in the aging population: comparison of risk factors in a 9-year prospective study. *American Journal of Geriatric Psychiatry* 17, 642–652.
- Vuillemenot, P., Richardson, M.P., Armony, J.L., Driver, J., Dolan, R.J., 2004. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature Neuroscience* 7, 1271–1278.
- Watkins, L.L., Grossman, P., Krishnan, R., Sherwood, A., 1998. Anxiety and vagal control of heart rate. *Psychosomatic Medicine* 60, 498–502.
- Watson, D., Clark, L.A., 1984. Negative affectivity – the disposition to experience aversive emotional states. *Psychological Bulletin* 96, 465–490.
- Watson, D., Hubbard, B., 1996. Adaptational style and dispositional structure: coping in the context of the five-factor model. *Journal of Personality* 64, 737–774.
- Widiger, T.A., Hurt, S.W., Frances, A., Clarkin, J.F., Gilmore, M., 1984. Diagnostic efficiency and DSM-III. *Archives of General Psychiatry* 41, 1005–1012.
- Williams, J.M.G., Mathews, A., MacLeod, C., 1996. The emotional stroop task and psychopathology. *Psychological Bulletin* 120, 3–24.
- Wilson, G.D., Kumari, V., Gray, J.A., Corr, P.J., 2000. The role of neuroticism in startle reactions to fearful and disgusting stimuli. *Personality and Individual Differences* 29, 1077–1082.
- Wolfensberger, S.P.A., Veltman, D.J., Hoogendoorn, W.J.G., Boomsma, D.I., de Geus, E.J.C., 2008. Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. *Neuroimage* 41, 544–552.

- Wüst, S., Federenko, I., Hellhammer, D.H., Kirschbaum, C., 2000. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology* 25, 707–720.
- Yoshino, A., Kimura, Y., Yoshida, T., Takahashi, Y., Nomura, S., 2005. Relationships between temperament dimensions in personality and unconscious emotional responses. *Biological Psychiatry* 57, 1–6.
- Young, E.A., Abelson, J., Lightman, S.L., 2004. Cortisol pulsatility and its role in stress regulation and health. *Frontiers in Neuroendocrinology* 25, 69–76.
- Zautra, A.J., Affleck, G.G., Tennen, H., Reich, J.W., Davis, M.C., 2005. Dynamic approaches to emotions and stress in everyday life: Bolger and Zuckerman reloaded with positive as well as negative affects. *Journal of Personality* 73, 1511–1538.
- Zobel, A., Barkow, K., Schulze-Rauschenbach, S., Von Widdern, O., Metten, M., Pfeiffer, U., Schnell, S., Wagner, M., Maier, W., 2004. High neuroticism and depressive temperament are associated with dysfunctional regulation of the hypothalamic–pituitary–adrenocortical system in healthy volunteers. *Acta Psychiatrica Scandinavica* 109, 392–399.
- Zuckerman, M., 2003. Biological bases of personality. In: Millon, T., Lerner, M. (Eds.), *Handbook of Psychology: Personality and Social Psychology*, vol. 5. John Wiley & Sons, Inc, New York, pp. 85–116.