Mood related insights : functional and structural MRI studies in depression and anxiety disorders

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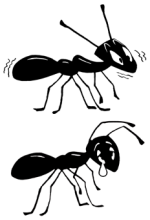

CHAPTER 7

AFFECTIVE PERSONALITY TRAITS ARE LINKED TO VOLUME OF THE ORBITOFRONTAL CORTEX AND AMYGDALA

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SUMMARY

Background: Neuroticism and extraversion are personality factors associated with the development of affective disorders, possibly through differential impact on brain structures implicated in emotional processing. To date, studies on brain morphology mainly focussed on neuroticism, yielding conflicting findings concerning the association with personality, partially due to methodological issues and samples under study.

Methods: In the present study, high resolution structural T1-weighted MR images of 65 healthy adults were processed using an optimized Voxel Based Morphometry approach. Multiple regression analyses were performed to test for associations of neuroticism and extraversion with prefrontal and subcortical volumes.

Results: Orbitofrontal and right amygdala volume were both positively related to extraversion. Neuroticism scores not significantly correlated with these brain regions.

Conclusion: The present results indicate that the reduced likelihood on developing affective disorders associated with high extraversion may be related to modulation of emotion processing through the orbitofrontal cortex and the amygdala

Neuroticism and extraversion are personality factors that have been directly linked to emotional states: neuroticism has been associated with susceptibility to negative emotional states, whereas extraversion has been linked to susceptibility to positive emotional states (Larsen & Ketelaar, 1991). Also, neuroticism has been shown to correlate positively, whereas extraversion correlated negatively, with (subsyndromal) symptoms of depression and anxiety in the general population (Jylha & Isometsa, 2006). Other personality traits, such as agreeableness, openness to experiences, and conscientiousness have been proposed to play a more indirect role in influencing affective states (Larsen & Ketelaar, 1991). Consequently, neuroticism and extraversion may respectively put one at risk for (Bienvenu et al., 2004), or protect one against (Clark, Watson, & Mineka, 1994) development of affective disorders.

More insight in the relation between personality and brain regions associated with emotion processing and regulation may help to understand the influence of personality on the manifestation of subclinical anxiety and depression symptoms. On a functional level, it has previously been shown that neuroticism modulates neural activity in prefrontal and subcortical brain regions related to affective processing (Canli, 2004; Cremers et al., 2010). Neuroticism has been related to more amygdala activation in response to distracting negative facial expressions during a cognitive task (Haas, Omura, Constable, & Canli, 2007) and to less anterior cingulate cortex–amygdala connectivity during processing of negative emotional facial expressions (Cremers et al., 2010). Extraversion on the other hand, was found to be positively associated with amygdala activation in response to happy faces (Canli, 2004). Together, these findings indicate that core brain structures involved in emotion processing, such as the amygdala and the ventral part of the prefrontal cortex, including the orbitofrontal cortex, may play a role in the relation between personality and affective behaviour.

Structural variation might underlie these functional relations of personality and regions related to emotion perception and appraisal. In an adolescent sample, an association between extraversion, but not neuroticism, and prefrontal volume (Blankstein, Chen, Mincic, McGrath, & Davis, 2009) has been observed, which has also been demonstrated in adults (DeYoung et al., 2010), although not consistently (Wright et al., 2006). Therefore, the relation between brain volume and affect related personality traits remains unclear. Inconsistencies in reported findings may be due to methodological and technical issues, such as the use of different segmentation and normalization strategy (e.g. analysis based on modulated vs unmodulated images (Omura, Todd Constable, & Canli, 2005)), not accounting for total brain volume (Gardini, Cloninger, & Venneri, 2009), or to sample characteristics and processes of brain maturation (e.g. by including only elderly (Jackson, Balota, & Head, 2009; Wright, Feczko, Dickerson, & Williams, 2007) or only adolescents (Blankstein et al., 2009). Aging is an important predictor of regional brain volume, and the process of aging (including brain maturation) has been shown to interact with

personality (Jackson et al., 2009). It is therefore necessary to further elucidate the complex relation between affect related personality traits and regional brain volume in an adult sample, controlling for these important factors. In the present study, we used an optimized voxel based morphometry approach to investigate the relationship between neuroticism, extraversion, and regional brain volume in a large sample of healthy adults. We focussed on brain regions involved in the initial processing of emotional information (amygdala) and on regions related to the appraisal and decision making influence of emotional information, (anterior cingulate cortex and orbitofrontal cortex) (Drevets et al., 2008). As such, we aimed to identify neuro-anatomical substrates associated with affect-related personality traits.

METHODS

ETHICS STATEMENT

The study was carried out in accordance with the Declaration of Helsinki. Also, the Ethical Review Boards of the Leiden University Medical Center, Academic medical Center Amsterdam, and University Medical Center Groningen approved this study. All participants provided written informed consent after complete description of the study.

PARTICIPANTS

Sixty-five healthy control participants were selected from the NESDA (Netherlands Study of Depression and Anxiety) neuroimaging study (Penninx et al., 2008). The MRI main sample is described in detail elsewhere (van Tol et al.,2010). Exclusion criteria for the current sample were: 1) a history of or current DSM IV axis I pathology, 2) taking any psychoactive drugs, 3) the presence or history of major internal or neurological disorder, 4) dependency or recent abuse (past year) of alcohol and/or drugs, 5) hypertension 6) general MR-contraindications.

PERSONALITY QUESTIONNAIRE

To asses personality traits, all participants completed the NEO Five Factor Inventory (Costa & McGrae, 1992).

IMAGE ACQUISITION

Imaging data were acquired using Philips 3-tesla MR-systems (Best, The Netherlands) located at the Leiden University Medical Center (LUMC), Academical Medical Center (AMC) University of Amsterdam, and University Medical Center Groningen (UMCG), equipped with a SENSE-8 (LUMC and UMCG) and a SENSE-6 (AMC) channel head coil, respectively. For each subject, anatomical images were obtained using a sagittal 3D gradient-echo T1-weighted sequence (TR=9 ms, TE=3.5 ms; matrix 256x256; voxel size: 1x1x1mm; 170 slices).

DATA ANALYSIS

Voxel Based Morphometry (VBM) following the Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) algebra software (Ashburner, 2007) implemented in Matlab 7.1.0 (The MathWorks Inc., Natick, MA, USA) was used. The preprocessing and masking procedure is described in detail elsewhere (van Tol et al., 2010). Briefly, after segmentation, data were registered, normalized, and modulated using the DARTEL pipeline. Gray matter (GM) images were normalized to Montreal Neurological Institute (MNI) space and smoothed at 8 mm full width at half maximum (FWHM). In the resulting images, each voxel represents an absolute amount of brain volume, equivalent to the brain volume per unit prior to normalization.

Next, we performed a regression analysis with neuroticism and extraversion as independent variables. Age, gender, scan center, and gray matter total volumes were entered as nuisance variables. Based on the literature on emotion processing in affective disorders (Drevets et al.,2008), we set the following regions of interest (ROI): amygdala, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC). Results are reported at $p<.05$ Family wise error (FWE) corrected for the spatial extent of the ROIs (small volume corrections). The ROIs were defined by the Automated Anatomical Labeling (AAL) templates implemented in the Wake Forest University (WFU) pickatlas (Maldjian et al., 2003). For regions other than the ROI's, a voxel level threshold of $p<.05$ whole brain FWE corrected was set a priori. Demographic and clinical data were analyzed with SPSS 16.0 (SPSS Inc., Chicago, Il, USA) and significance was set at $p<.05$.

RESULTS

SAMPLE CHARACTERISTICS AND PERSONALITY SCORES

The age range of the 65 participants (42 females) was: 21-56, Mean (M) =40.5, standard deviation (sd) =9.7; years of education: M=14.3, sd=2.9). Neuroticism (range= 13-36; M=24.2, sd=4.9) correlated negatively to extraversion (range 27-56; M=43.7, sd=6.2) (r =-0.4, $p<.05$) and total gray matter volume (r =-0.3, $p<.05$). Extraversion was positively correlated to total gray matter volume (r =0.3, p<.05). No correlation was observed between neuroticism or extraversion and age, years of education, and sex (all $p>.13$).

PERSONALITY AND REGIONAL BRAIN VOLUME

The right orbitofrontal cortex (BA 11; MNI coordinates: [x=13 y=16 z=-14], Z=3.77, clustersize= 329) and right amygdala (MNI coordinates: [x=21 y=-10 z=-21], Z=3.34, clustersize= 31)) showed a positive relation with extraversion. Neuroticism did not show a significant relation with regional brain volume in any of our regions of interest. Adding the other three personality variables (openness, agreeableness, and conscientiousness) from the NEO_FFI did not significantly change the results (orbitofrontal cortex: Z=3.28; amygdala, Z=3.50). Results are showed in figure 1.

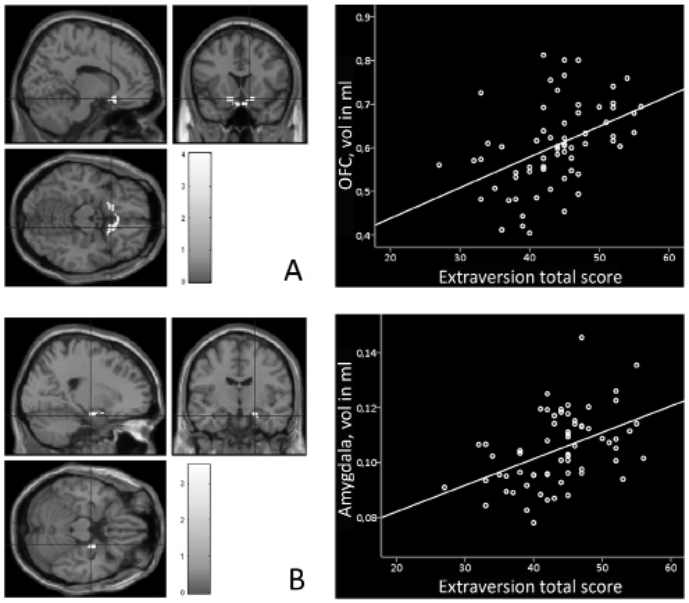

FIGURE 1: CORRELATIONS OF NEUROTICISM AND EXTRAVERSION IN THE AMYGDALA AND OFC

A) Positive correlation of extraversion and volume of the right orbital frontal gyrus

B) Positive correlation of extraversion and right amygdala volume.

Correlations of extraversion with volume of the orbitofrontal cortex and amygdala are overlayed on the mean high-resolution T1-weighted template in MNI space at $p<.005$ for display purposes.

DISCUSSION

In the present report, we used an optimized VBM approach to test for personality related variations in regional brain volume, while controlling for age and gender, and demonstrated a positive correlation of extraversion and OFC and amygdalar volume in an adult sample. This result confirms the role of the OFC in personality, a region that was already associated with personality changes in the case report of Phineas Gage (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). We also found a positive correlation between extraversion and volume of the amygdala. However, we did not find strong structural correlates of neuroticism.

The observation that extraversion correlated positively with volume of both the OFC and amygdala is of interest because of the role these regions play in affective processing (Rolls, 2004; Rolls & Grabenhorst, 2008). The OFC has often been associated with controlling reward and punishment related behavior, emotion regulation, and decision making (Kringelbach & Rolls, 2004). The amygdala has a well-documented role in emotion processing and has bi-directional connections with the OFC (Price, 2003). Interestingly, a positive correlation of OFC thickness with extraversion and fear extinction has been described in a small study (Rauch et al., 2005). In another study, humor-driven activation, reflecting hedonic capacity, was found to be positively correlated

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with extraversion in the right OFC (Mobbs, Hagan, Azim, Menon, & Reiss, 2005). In the amygdala, activation during happy face viewing was found to be positively related to extraversion (Canli, 2004). Hence, the increased volumes of OFC and amygdala may play a role in the increased sensitiveness to positive, pleasant information and (social) reward, and the propensity to experience positive affect which characterizes extraversion (Clark et al., 1994). The nature of this role, however, awaits further elucidation, as increased volumes of GM in brain areas may be reflective of processes involving amongst others glia cells, inhibiting or excitatory interneurons, and neurons. However, these processes can not be assessed directly in vivo.

The present result is in line with findings of Blankenstein and colleagues (2009) who used a similar methodology (i.e. an optimized VBM approach) in an adolescent sample. The present results are also in line with results of previous studies that have shown a relation between personality and orbitofrontal cortical thickness (Wright et al., 2006) and lateral PFC volume (Wright et al., 2007) in smaller samples of young adults and elderly. However, Wright and colleagues (2006) reported that neuroticism was negatively related to OFC volume and extraversion was positively related to lateral PFC volume in a young adults. Accordingly, in the present study, we expected neuroticism to account for a substantial portion of the volumetric variation in regions associated with emotional perception and regulation. However, no such relation was observed. Instead, extraversion was found to be the main predictor of regional brain volume in affective brain regions. Discrepancy in findings might be due to methodological issues such as outlined before; in this study we used an optimized VBM method in a relatively large adult subject sample.

In the present study we examined structural correlates of extraversion and neuroticism in a cross-sectional design. Therefore, it is possible that the found correlates are not primary, but secondary to individual personality characteristics. For instance, high extraversion is known to be associated with different lifetime experiences than low extraversion. As of yet unpublished finding from the same NESDA study indicate that extraversion and negative life events mediate the course of depressive symptoms (Spinhoven et al. 2011). Extraversion and lifetime experiences may also lead to a differential effect on brain structures involved in social interaction or hedonia.

Given the augmenting evidence for a significant relation between extraversion and OFC and amygdala volumes, it will be important to further elucidate this relation in studies addressing structural and functional connectivity of the OFC and the amygdala. This would also provide more insight the trajectory from health to psychopathology, and as such identify neuroanatomical markers for the risk of affective disorders.