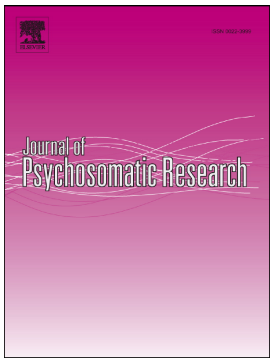

Cortico-striatal-thalamic loop as a neural correlate of neuroticism in the mind-body interface

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Cortico-striatal-thalamic loop as a neural correlate of neuroticism in the mind-body interface

Running head: Cortico-striatal-thalamic loop in neuroticism

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Abstract

Objective

Although brain structural studies have demonstrated the neural correlates of neuroticism, the outcomes are not easily identified because of the various possible brain regions involved, low statistical power (low number of subjects), and brain structural measures available, such as mean diffusivity (MD), which are more suitable than standard regional measures of grey and white-matter volume (rGMV, rWMV) and fractional anisotropy (FA). We hypothesized that neuroticism neural correlates could be detected by MD and differentially identified using other measures. We aimed to visualize the neural correlates of neuroticism.

Methods

A voxel-by-voxel regression analysis was performed using the MD, rGMV, rWMV, or FA value as the dependent variable and with neuroticism scores based on the NEO-FFI and its confounding factors as independent variables in 1207 (693 men and 514 women; age, 20.7 ± 1.8, 18-27 years), non-clinical students in a cross-sectional study.

Results

MD in the cortico- (orbitofrontal cortex, anterior cingulate cortex, and posterior insula) striatal- (caudate and putamen) thalamic loop regions, including the right posterior limb of the internal capsule, were positively associated with neuroticism using the threshold-free cluster

enhancement method with a family-wise error-corrected threshold of $P < 0.0125$ (0.05/4, Bonferroni correction for four types of MRI data [MD, rGMV, rWMV, and FA]) at the whole-brain level.

Conclusions

An increased MD has generally been associated with reduced neural tissues and possibly area function. Accordingly, this finding helps elucidate the mechanism of somatization in neuroticism because the regions related to neuroticism are considered neural correlates of somatoform disorders.

Key words: cortico-striatal-thalamic loop; mean diffusivity; neuroticism; posterior limb of the internal capsule

Introduction

Neuroticism is defined as an inability to deal with negative emotions [1], it predicts common mental disorders [2], e.g., affective disorders [3], social anxiety disorders [4], and poor sleep [5]. Further, lower levels of neuroticism are related to subjective well-being [6]. Critically, couples high in neuroticism experience lower levels of marital satisfaction [7]. Clinically, psychosomatic theories have often identified neuroticism as a causal influence of the development of disease [8]. Indeed, in a population-based cohort study, neuroticism was associated with self-reported somatic symptoms [9, 10]. Thus, neuroticism causes mental and physical disorders.

The neural mechanisms underlying individual differences in neuroticism might elucidate the mechanism of the neuroticism causing mental and physical disorders. Regarding brain studies about neuroticism, there is no obvious specified region. Based on structural MRI data, the parietal cortical thickness variations were related to neuroticism in 56 young women [11], whereas a significant interaction among neuroticism, age, and sex on the thickness of the anterior cingulate cortex (ACC) was found in 450 subjects (19-80 years of age) [12]. Using intracortical myelin levels, neuroticism was negatively related to the frontal pole and positively related to the occipital cortex in 1003 individuals (mean age: 29 years) [13]. Higher neuroticism was significantly associated with lower uncinate fractional anisotropy (FA) bilaterally in 1091

older subjects with a mean age of 70 years [14]. Using resting-state functional MRI data, neuroticism was shown to be correlated with the parietal cortex system in 49 adults (19-52 years) [15], whereas neuroticism was negatively associated with both the ventral and dorsal attention networks in 365 participants (20-80 years of age) [16].

Mean diffusivity (MD) and FA measure are standard related parameters of diffusion tensor imaging (DTI). Importantly, MD in areas of the dopaminergic system is associated with various dopaminergic system functions and is related to personality traits such as harm avoidance and self-directedness [17]. In one study, neuroticism scores were positively correlated with MD in the anterior cingulum and uncinate fasciculus in 51 participants (18-54 years) [18]. However, the sample was small, and the study focused on white matter [18].

Linear decreases in neuroticism over time have been observed in people aged 18 to 25 years [19], although age-related differences appear to be somewhat more pronounced before age 30 than after [20].

Accordingly, we hypothesized that the neural correlates of neuroticism could be comprehensively detected by MD and might be differentially detected using distinct brain structure measures in young adults. The purpose of this study was to test this hypothesis and detect the neural correlates of neuroticism in a large sample.

We used the Japanese version of the Neuroticism, Extraversion, Openness- Five Factor

Inventory (NEO-FFI) i.e., a Big Five personality measure that incorporates both normal and abnormal personality traits [21]. The NEO-FFI assess general personality traits and is used in a wide variety of settings around the world in over 40 authorized translations [21]. We focused on neuroticism, as it is regarded as negative emotion and leads to psychological distress [2-5], unlike the other three personality traits (extraversion, openness to experience, agreeableness, and conscientiousness) as positive ones.

Materials and Methods

Subjects

The present study is a part of an ongoing project to investigate the associations among brain imaging findings, cognitive functions, and psychological data and included 1207 healthy, right-handed individuals (693 men and 514 women) with a mean age of 20.7 ± 1.8 (18-27) years. Clinical data were not included in this project. The following descriptions are reproduced mainly from one of our previous studies of the same ongoing project using the same methods [22]. Each participant was paid 1,000 yen per hour in compensation for their time and effort. All subjects were university, college, or postgraduate students who had graduated from their respective institutions within 1 year of the initiation of our experiment. Japanese schools typically provide annual health check ups. After the participants complete the health

examination, the Health Administration Center is available to help with retesting, explain the results, and provide health-related guidance and hospital referrals [23]. We also distributed self-report questionnaires to potential subjects to assess their history of psychiatric and physical illness as well as their recent drug use [24]. The assessments performed during and after recruitment were voluntary and self-reported. During the recruitment procedure, the exclusion criteria, including a restriction on individuals with physical or mental health conditions, were explained to all subjects. Potential subjects were reminded of the exclusion criteria after the preliminary contact to prevent individuals who should have been excluded from the study from arriving at the laboratory to participate. Accordingly, all the subjects had normal vision, and none of the subjects included in our study had a history of neurological or psychiatric illnesses. Written informed consent was obtained from each participant prior to beginning the study in accordance with the Declaration of Helsinki (1991). All study procedures were approved by the Ethics Committee of Tohoku University. The ethics approval number is 2019-1-605. All experiments were performed in accordance with approved guidelines. For more details regarding the procedures undertaken in the present study, please refer to our previous work [22].

Psychological Outcome Measures

Assessment of neuroticism

To assess the neuroticism of the subjects, all of them were asked to complete a 60-item Japanese version (5-point scale) of the NEO-FFI [8]. Neuroticism traits were previously described as follows [25]: the tendency to experience negative emotions and psychological distress in response to stressors. For more details, please refer to our previous study [26].

Psychometric measures of general intelligence

The Raven's Advanced Progressive Matrix (RAPM), a widely used measure of general intelligence [27], was utilized in the present study as a covariate in neuroimaging analyses, as described in a previous study [28]. The test contains 36 nonverbal items requiring fluid reasoning ability. Each item consists of a 3 × 3 matrix with a missing piece to be completed by selecting the best of 8 alternatives. The score of this test (number of correct answers in 30 min without measuring reaction time) was used as a psychometric index of individual intelligence. This measure was adjusted to assess the effects of general intelligence on brain structures [29-31].

Behavioural data analyses

All behavioural data were analysed using the IBM SPSS Statistics 22.0 software package (IBM

Corp.; Armonk, NY, USA). Differences between males and females in terms of age and scores on the measures (RAPM, neuroticism scores) were analysed by a 2-sample t-test; a two-tailed *P*-value < 0.05 was considered to indicate statistical significance.

Image Acquisition

Structural MRI

All MRI data were acquired using a 3T Philips Achieva scanner (Philips Medical Systems, Best, Netherlands). Three-dimensional high-resolution T1-weighted images were collected using a magnetisation-prepared rapid gradient-echo sequence with the following parameters: 240 × 240 matrix, TR = 6.5 ms, TE = 3 ms, TI = 711 ms, FOV = 24 cm, slices = 162, in plane resolution = 1.0 × 1.0 mm, slice thickness = 1.0 mm, and scan duration = 483 s.

Diffusion-weighted data were acquired using a spin-echo echo-planar imaging (EPI) sequence with the following parameters: TR = 10293 ms, TE = 55 ms, FOV = 22.4 cm, 2 × 2 × 2 mm^3 voxels, slices = 60, SENSE reduction factor = 2, and number of acquisitions = 1. Diffusion weighting was isotropically distributed in 32 directions (*b* value = 1,000 s/mm^2), and three images with no diffusion weighting (*b* value = 0 s/mm^2; b = 0 images) were acquired using the spin-echo EPI sequence (TR = 10293 ms, TE = 55 ms, FOV = 22.4 cm, 2 × 2 × 2-mm^3 voxels, slices = 60). Acquisitions for phase correction and signal stabilization were performed, although

these data were not used for image reconstruction. For more details regarding these procedures, please refer to our previous work [32, 33].

Pre-processing and Analyses of Structural Data

Voxel-based morphometry (VBM) data

All pre-processing of the T1-weighted images data was performed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK) according to the protocol described for VBM analyses in a previous report from our group [34]. Using the new segmentation algorithm implemented in SPM12, T1-weighted structural images from each individual were segmented and normalized to Montreal Neurological Institute (MNI) space to yield images with 1.5 x 1.5 x 1.5 mm voxels using the diffeomorphic anatomical registration through the exponentiated lie algebra (DARTEL) registration process implemented in SPM12. In addition, we performed a post hoc volume change correction (modulation) [35]. All images were smoothed by convolving them using an isotropic Gaussian kernel of 6 mm full-width at half maximum (FWHM). For additional details, please refer to our previous work [34].

MD and FA data

All pre-processing and analyses of the imaging data were performed using SPM8 implemented in MATLAB (MathWorks Inc.; Natick, MA, USA). The methods and parameters were optimized and validated using SPM8 since those using SPM12 were not validated in our previous study [32]. Most of the following descriptions were reproduced from our previous study using similar methods [36].

The MD map was calculated from the collected images using a commercially available diffusion tensor analysis package (Philips Medical Systems, Best, Netherlands) utilizing the MR console. These procedures involved corrections for motion and distortion caused by eddy currents, and all calculations were performed using a previously described method [37]. Briefly, the MD images from participants were normalized using a previously validated registration through a DARTEL-based registration process that utilized the information of the FA signal distribution within the white-matter tissue and all images including grey matter segments (regional grey matter density [rGMD] map), white-matter segments (regional white-matter density [rWMD] map), and cerebrospinal fluid (CSF) segments (regional CSF density [rCSFD] map) of diffusion images. The voxel size of these normalized images was 1.5 × 1.5 × 1.5 mm voxels. Next, tissues that were least likely to be grey or white matter were manually removed, and the images were smoothed by convolving them using an isotropic Gaussian kernel of 8-mm FWHM.

Normalized FA images were then masked by a custom mask image most likely to be white matter and then smoothed by a Gaussian kernel of 8 mm FWHM. For additional details, please refer to our previous work [36].

Statistical Group-level Analyses of Imaging and Behavioural Data

Correction for multiple comparisons was performed using threshold-free cluster enhancement (TFCE) [38] with randomised (5,000 permutations) nonparametric testing in the TFCE toolbox (http://dbm.neuro.uni-jena.de/tfce/). An FWE-corrected threshold of $P < 0.0125$ (0.05/4; Bonferroni correction for four types of MRI data [MD, rGMV, rWMV, and FA]) was applied. For more details, please refer to a previous study by our group [39].

VBM data

A whole-brain multiple regression analysis was performed in SPM12 and used to assess the association between rGMV (or rWMV) and neuroticism scores. Covariates for this analysis included sex, age, RAPM score, and total intracranial brain volume (TIV). For each covariate, the overall mean was used for mean centring. Analyses for rGMV (or rWMV) were performed in voxels for all subjects that showed a signal intensity >0.05.

We also investigated whether the relationship between rGMV (or rWMV) and neuroticism

scores differed between males and females at the whole-brain level. We employed a voxel-wise ANCOVA in which sex difference was a group factor, using *t*-contrasts (using the full factorial option of SPM12). In this analysis, age, RAPM, TIV, and neuroticism score were modelled to enable detection of unique relationships with rGMV (or rWMV) (using the interaction option in SPM8 for each sex). TIV was modelled to have a common relationship with rGMV (or rWMV) across both sexes.

DTI (FA and MD) data

A voxel-by-voxel regression analysis was performed in SPM8 using the FA or MD value with each voxel as the dependent variable and with age, sex, RAPM score, and neuroticism scores as independent variables. The analysis using FA was limited to areas within white matter, whereas the analysis using MD was limited to areas within the grey- and white-matter masks created using the procedures described above. We also investigated whether the relationship between FA or MD and each score of neuroticism differed between men and women by using the same method as that used for rGMV.

Results

Behavioural Data

Table 1 shows the means and standard deviations (SDs) for age, the RAPM scores, and neuroticism. Figure 1 depicts the distributions of the scores in males and females. The average age (± standard deviation) was 20.8 (1.8), 18-27 years in males (N = 693) and 20.6 (1.6), 18-27 years in females (N = 510). There were significant differences between males and females in RAPM and neuroticism scores ($P < 0.01$, a 2-sample t-test).

MRI Data

VBM data

After controlling for sex, age, and TIV (total GM volume + total WMV + total CSF volume), and RAPM scores, there were no significant positive or negative correlations between neuroticism scores and regional rGMV (rWMV) at each voxel using an FWE-corrected threshold of $P < 0.0125$ (0.05/4; Bonferroni correction for four types of MRI data [MD, rGMV, rWMV, and FA]), based on the TFCE method at the whole-brain level.

Analysis of DTI (FA and MD) data

A whole-brain multiple regression analysis that was performed after controlling for sex, age, TIV, and RAPM scores revealed no significant correlation between neuroticism scores and FA

using the TFCE method with an FWE-corrected threshold of $P < 0.0125$ (0.05/4; Bonferroni correction for four types of MRI data [MD, rGMV, rWMV, and FA]) at the whole-brain level.

We found a significant positive correlation between neuroticism scores and MD of the right posterior limb of the internal capsule (PLIC) (including the thalamus, caudate body, and posterior insula), ACC, prefrontal cortex (PFC), and inferior frontal gyrus (IFG) using the same analyses described above using the TFCE method with an FWE-corrected threshold of $P < 0.0125$ (0.05/4) at the whole-brain level (Table 2 and Figure 2).

Interaction effects of sex and neuroticism on brain structures

Using data from both sexes with respect to the covariates of age, TIV, and RAPM scores, an analysis of covariance (ANCOVA) revealed no significant interaction effect between neuroticism scores and sex on rGMV, rWMV, FA, or MD using the TFCE method with an FWE-corrected threshold of $P < 0.0125$ (0.05/4, Bonferroni correction for four types of MRI data [rGMV, rWMV, FA, and MD]) at the whole-brain level. These results were not in accordance with our behavioural results and the significant differences between males and females and neuroticism scores ($P < 0.01$, a 2-sample t-test).

Discussion

The present study investigated comprehensive associations between neuroticism and brain structures in non-clinical data of a large sample of young individuals at the whole-brain level using robust statistical thresholds. Surprisingly, neuroticism scores were positively related to regional MD values of the right PLIC (including the thalamus, caudate body, and posterior insula), ACC, orbitofrontal cortex (OFC), and IFG, including the orbital part. These regions consist of the cortico-striatal-thalamic loop. This outcome detected only by MD was partly consistent with our hypothesis that the neural correlates of neuroticism could be comprehensively detected by MD.

First, we should outline potential mechanisms of the cortico- (OFC and ACC) striatal- (caudate and putamen) thalamic loop as a critical neural correlate of neuroticism. The cortico- (OFC and ACC) striatal projection shows abnormal activity in psychiatric disease, and normalization of activity in these regions has been associated with a therapeutic response to a variety of pharmacological, behavioural, and electrical treatments [40]. Recruitment of central thalamic neurons occurs in response to increasing cognitive demand, stress, fatigue, and other perturbations that reduce behavioural performance [41]. Many symptoms of anxiety disorders, especially obsessive-compulsive disorder, are related to disruptions within the orbitofronto-striatal-thalamic-cortical loop [42]. Further, there is synchrony of change between anxiety and pain [43]. Anatomically, the PLIC carries thalamo-cortical and corticospinal fibres

[44]. Ascending and descending fibre tracts course within the internal capsule to connect the cerebral hemispheres with subcortical structures [45]. Damage to the PLIC leads to poor motor outcomes because the corticospinal tract is located in the PLIC [46]. Interestingly, WM tracts, including those of the PLIC, contribute to worry prediction [47]. Furthermore, the PLIC is a robust correlate and predictor of many physical disorders [48]. We should emphasize why the 'right and posterior' limb of the internal capsule was significantly correlated with the degree of neuroticism. The corticospinal tract is located in the posterior limb of the internal capsule, not the anterior limb [46]. Importantly, touch and tactile neuropathic pain sensitivity are set by corticospinal projections [49]. As for laterality, chief somatic symptoms presented significantly more on the left side than on the right side of the body [50]. Furthermore, the sensitivity to detect transient nociceptive stimuli was higher for the left hand than the right hand for right-handed subjects [51]. As we mentioned in the Methods, all of the subjects in this study were right-handed. Accordingly, it seems natural that not the left but the right PLIC was detected as the neural correlate of neuroticism since the right PLIC possesses the direct neurotic fibre via corticospinal fibres to left peripheral nerves leading to left hemisphere somatoform symptoms. Interestingly, the grey matter density of the putamen was linked to dispositional optimism (i.e., opposite disposition of neuroticism) [52]. Thus, the cortico- (OFC and ACC) striatal- (caudate and putamen) thalamic loop seems to be connecting the mind-body interface in

somatization in accordance with the fact that patients with anxiety disorders usually have many somatoform complaints.

Second, our findings could explain why the posterior insula was also detected as a neural correlate of neuroticism. This result was in line with a previous study showing that the degree of insula activation was related to the subjects' degree of neuroticism as measured by the Big Five personality measure during a risk-taking decision-making task using functional MRI [53]. The posterior insula showed high activity while a person was anticipating pain [54]. The primary interoceptive representation in the dorsal posterior insula engenders distinct highly resolved feelings from the body that include pain, temperature, muscular and visceral sensations, and vasomotor activity [55]. Furthermore, the right posterior insula underpins the subjective experience of body ownership [56]. Thus, the insula might also connect the mind-body interface in somatization.

Third, our findings should explain why only MD could demonstrate a significant association with neuroticism. As we mentioned in the Introduction, MD in areas of the dopaminergic system, particularly in subcortical areas including the basal ganglia, is associated with various dopaminergic system functions. MD represents not only properties of white matter but also those of grey matter [17]. Furthermore, the strength of our pre-processing method is the ability to obtain MD signals in grey matter areas, particularly in subcortical regions, which are known

to be important in traits with dopaminergic function such as harm avoidance and self-directedness [17]. Moreover, MD and FA measures are distinct microstructural brain properties. In particular, MD assesses capillaries, spines, macromolecular proteins, myelin properties, membranes, axons, neuron shapes, protoplasmic and fibrous glia, and enhanced tissue organization [17, 33]. Furthermore, FA values are more stable from adolescence to middle age than MD values [57]. This difference in the degree of change over time might affect the sensitivity of FA and MD regarding the detection of regions associated with personality [58]. Finally, we should mention the limitations of this study. As we have previously noted [32], due to the cross-sectional design, the results presented here cannot be used to determine causality between personality scores and associated brain regions. Furthermore, we used young, highly educated, healthy Japanese subjects, which may have affected the generalisability of our findings. For example, the magnitude of neuroticism might not allow for the detection of the primary sensory or motor areas, which could induce somatoform disorders in clinical cases. Concerning nationality, decreases in neuroticism may be more pronounced and exhibit greater fluctuation in the level of all of the Big Five personality traits among healthy Japanese individuals than among American subjects [59]. Ageing reduces somatic pain sensitivity for pain intensities with less stimulation of the internal capsule, and the observed outcome in the PLIC might be limited in younger generations [60]. However, women, on average, have

significantly higher neuroticism scores, which is in accordance with previous findings [61] across most nations [62]. Further, after accounting for the various confounding variables, no true major difference in the prevalence of neurosis was confirmed [63].

Conclusions

This study showed comprehensive associations between neuroticism and brain structures in non-clinical data of a large sample of young individuals at the whole-brain level. Importantly, the results showed that neuroticism is related to reduced neural tissues in the regions of the cortico-striatal-thalamic loop. Further longitudinal investigations using more diverse samples are needed to examine the causality between neuroticism and the identified regions.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Author Contributions: S.N. H.T., Y.T. and R.K. designed the study. S.N., H.T., R.N., Y.K., T.S., T.M., A.S., K.I., R.Y., Y.Y., S.H., T.A., C.M.M., D.M., K.S., H.J., and Y.S. collected the data. S.N. and H.T. analysed the data and prepared the manuscript. All authors reviewed the manuscript.

Figure legends

Figure 1. Distribution of neuroticism scores in males and females.

Histograms show the distributions of neuroticism scores in males and females.

The average age (± standard deviation) was 20.8 (1.8), 18-27 years in males (N = 693) and 20.6 (1.6), 18-27 years in females (N = 510).

Figure 2. Regions correlated with mean diffusivity (MD) and neuroticism scores.

The present results were determined based on a family-wise error-corrected threshold of P < 0.0125 (0.05/4, Bonferroni correction for four types of MRI data [MD, rGMV, rWMV, and FA]) with threshold-free cluster enhancement (TFCE) based on 5000 permutations; the results were corrected at the whole-brain level. Regions showing correlations were overlaid onto a single T1 image in the SPM8 toolbox. The red-to-yellow colour scale indicates the level of the TFCE value's positive correlation with the MD and neuroticism scores; areas with significant correlations were identified in the right posterior limb of the internal capsule (including the thalamus, caudate body, and posterior insula) (A), left anterior prefrontal cortex (B), right caudate body (C), left inferior frontal gyrus (D), left orbital part of the inferior frontal gyrus (IFG) (E), and left anterior cingulate cortex (F).

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Table 1. Sex differences in age, RAPM scores, and neuroticism scores (mean ± SD): 2-sample t-test results.

Measure	Total	Males (N = 693)	Females (N = 510)	P	t
Age	20.7 (1.8)	20.8 (1.9)	20.6 (1.6)	0.035*	2.1
RAPM	28.5 (3.9)	28.8 (3.9)	28.1 (3.8)	0.002**	3.1
Neuroticism	28.1 (8.6)	27.5 (8.5)	28.9 (8.6)	0.004**	2.9

*$P < 0.05$, **$P < 0.01$.

Abbreviations: RAPM, Raven's Advanced Progressive Matrix; SD, standard deviation.

Table 2. Brain regions exhibiting a significant correlation between MD and neuroticism scores.

Brain region	R/L	x	y	z	*TFCE* *Value*	Corrected *P*-value (FWE)	Cluster size (k_E)
PLIC	R	23	-17	18	1535.9	0.008*	1116
		33	-12	17	1511.3	0.009*	
		30	-23	18	1508.5	0.009*	
Anterior PFC	L	-18	63	11	1433.3	0.010*	63
Caudate	R	15	5	18	1396.8	0.011*	107
IFG	L	-28	15	24	1391.1	0.011*	84
Orbital part of IFG	L	-32	32	-15	1352.6	0.012*	11
ACC	L	-6	36	6	1340.6	0.012*	5

FWE- corrected threshold of $^{*}P < 0.0125$ (0.05/4, Bonferroni correction for four types of MRI data [MD, rGMV, rWMV, and FA]) at the whole-brain level.

FWE: family-wise error, IFG: inferior frontal gyrus, L: left, PFC: prefrontal cortex, PLIC: posterior limb of inter capsule R: right, MD: rGMV: regional grey matter volume, rWMV: regional white matter volume, mean diffusivity, TFCE: threshold-free cluster enhancement.

Highlights

Neuroticism is related to reduced neural tissue in the cortico-striatal-thalamic loop

The orbitofrontal and anterior cingulate cortex, caudate and putamen are the regions

The posterior insula and posterior limb of the internal capsule includes the regions

The regions are considered neural correlates of somatoform disorders

Mean diffusivity values represent a certain loss of components of the tissue system

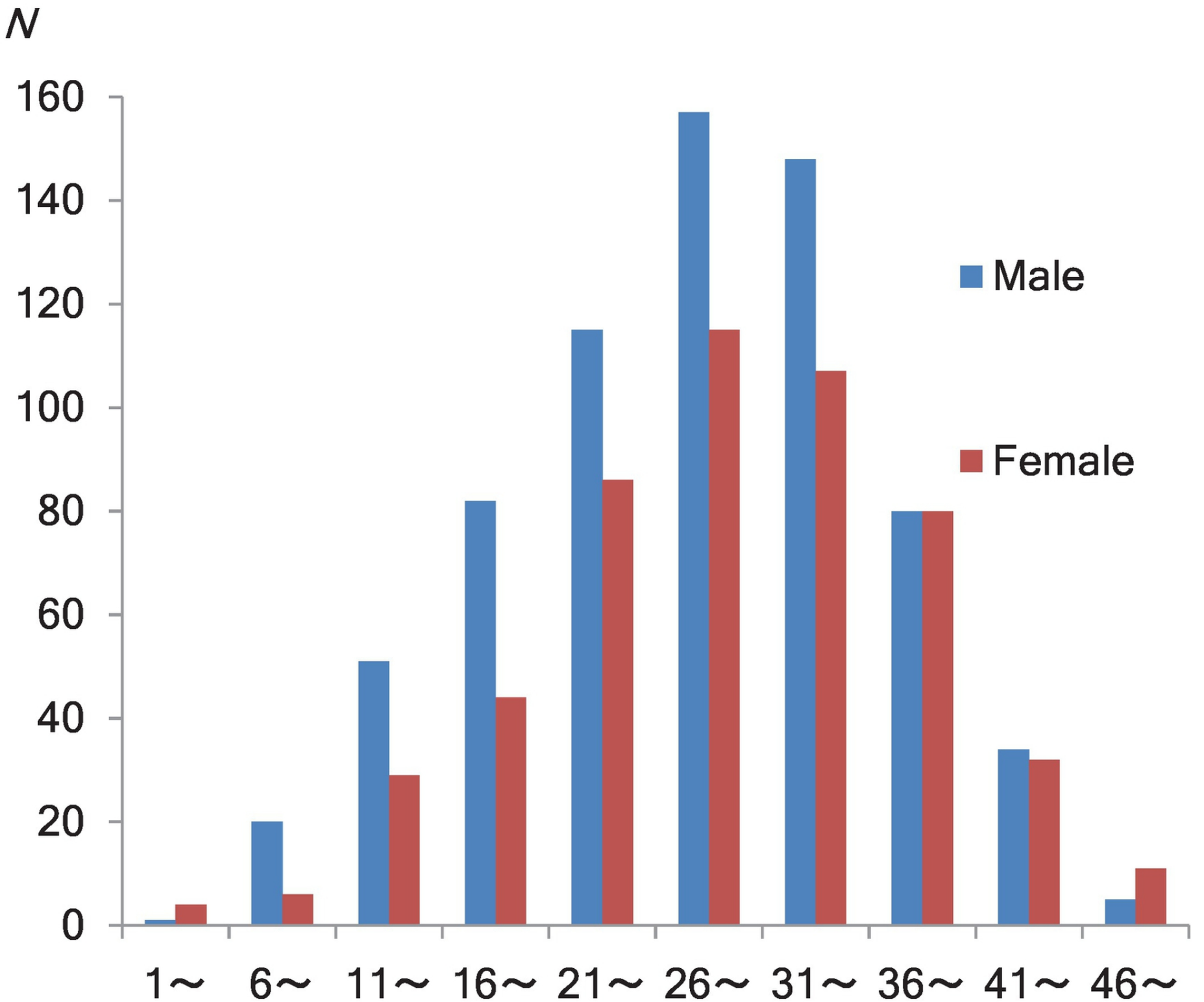
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Figure 1

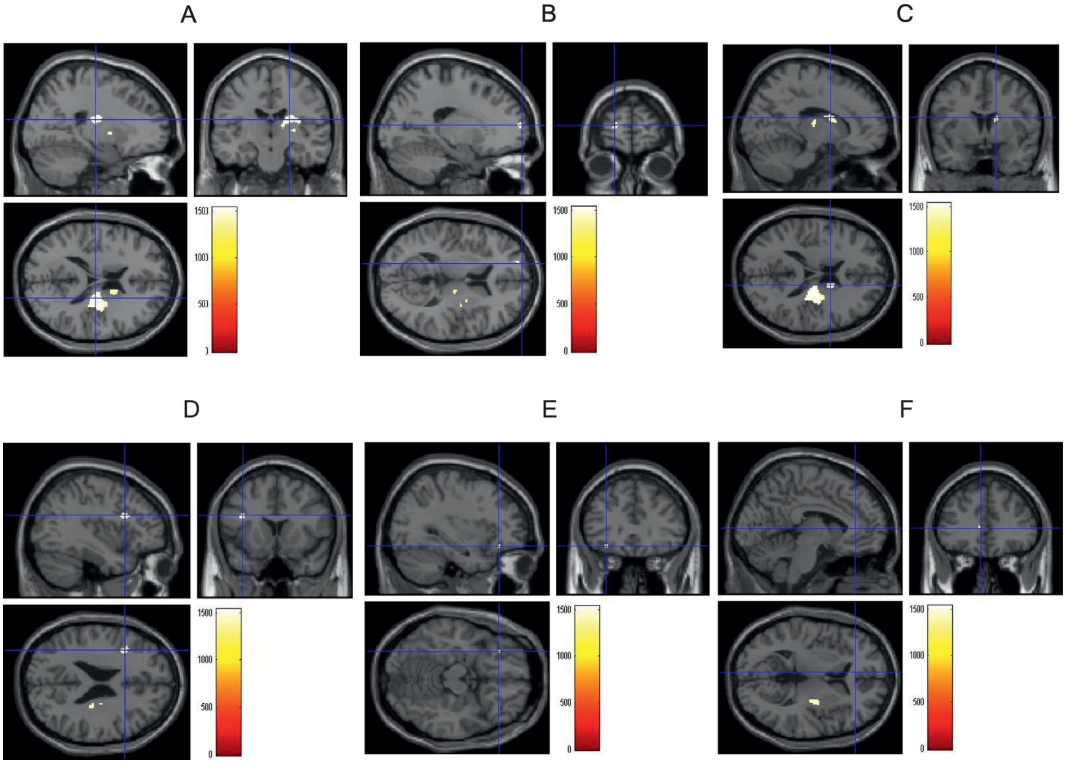

Figure 2