Journal of Affective Disorders 155 (2014) 169–173

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research Report

Association between affective temperaments and regional gray matter volume in healthy subjects

Koji Hatano [a,*], Takeshi Terao [a], Nobuhiko Hoaki [a], Kentaro Kohno [a], Yasuo Araki [a], Yoshinori Mizokami [a], Kensuke Kodama [a], Mayu Harada [a], Minoru Fujiki [b], Tsuyoshi Shimomura [b], Takuya Hayashi [c]

[a] *Department of Neuropsychiatry, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu City, Oita Prefecture 8795593, Japan*
[b] *Department of Neurosurgery, Oita University Faculty of Medicine, Oita, Japan*
[c] *Functional Architecture Imaging Unit, RIKEN Center for Life Science Technologies, Hyogo, Japan*

ARTICLE INFO

Article history:
Received 3 October 2013
Accepted 22 October 2013
Available online 30 October 2013

Keywords:
Cyclothymic temperament
Hyperthymic temperament
Left medial frontal gyrus
VBM
Healthy subject

ABSTRACT

Background: Affective temperaments such as cyclothymic and hyperthymic temperaments have been regarded as potential antecedents of bipolar disorder but the neural substrates underlying these temperaments have not been identified. The aim of this study is to determine whether these temperaments are associated with specific neural substrates in regional brain morphology in healthy subjects.
Methods: We conducted a cross-sectional neuroimaging study of 60 healthy subjects (30 males and 30 females) with affective temperaments. All participants underwent the Mini-International Neuropsychiatric Interview (MINI) to screen for the past and present psychiatric disorder. The scores of cyclothymic and hyperthymic temperaments were measured by the Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire. We analyzed the association between voxel-based morphometry of the brain and these affective temperaments.
Results: Subjects classified as having high cyclothymic scores had a significantly larger gray matter volume of the left medial frontal gyrus (MFG) than low cyclothymic subjects. High hyperthymic males also had significantly larger gray matter volume of the left MFG than low hyperthymic males, but there was no difference in females. Subjects with both high cyclothymic and high hyperthymic temperaments demonstrated significantly larger gray matter volume of the left MFG than their counterparts. Region of interest analysis revealed that peaks of these clusters showed a significant positive correlation of the regional volume with temperament scores.
Limitations: The subjects were relatively young and the number was relatively small. Due to the nature of a cross-sectional research design, we could not determine the causal relationship between temperament and the volume changes.
Conclusions: These findings suggest that cyclothymic and hyperthymic temperaments in healthy subjects may have their morphological basis in the left MFG.

1. Introduction

Affective temperaments such as cyclothymic and hyperthymic temperaments have been regarded as potential antecedents of bipolar disorder and they have been called bipolar temperaments. Cyclothymic temperament shows a central dimension that includes rapid fluctuations in mood and emotional instability, while hyperthymic temperament displays extroversion, a high energy level, emotional intensity and little need for sleep (Rovai et al., 2013). The modern concept of affective temperaments also assumes a continuum between these temperaments and bipolar disorder and is supported by a small but growing literature (Akiskal et al., 2005; Akiskal and Pinto, 1999; Ghaemi et al., 2001; Harnic et al., 2013; Takeshima and Oka, 2013). A recent longitudinal study of 57 patients with initial cyclothymia or bipolar disorder not otherwise specified diagnoses, showed that 42.1% progressed to a bipolar II diagnosis and 10.5% progressed to a bipolar I diagnosis (Alloy et al., 2012). As for pharmacotherapy, 36 depressive patients with cyclothymic and/or hyperthymic temperaments were likely to be in remission on lithium but not on selective serotonergic inhibitors (Goto et al., 2011), suggesting that bipolar temperaments in depression may affect drug response (Terao, 2012).

The neural substrates of affective temperaments have not been extensively investigated. It has been, however, shown that

* Corresponding author. Tel.: +81 97 586 5823; fax: +81 97 549 3583.
E-mail address: k-hatano@oita-u.ac.jp (K. Hatano).

0165-0327/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2013.10.045

cyclothymic scores in subjects with genetic risk of bipolar disorder were associated with the integrity of the bilateral internal capsules and the left temporal white matter (Sprooten et al., 2011). Recently, Serafini et al. (2011) reported that mood disordered patients with higher depressive, cyclothymic, irritable, anxious and lower hyperthymic temperament scores were likely to have greater white matter hyper-intensities than patients with higher hyperthymic temperament scores . Whereas Harada et al. (2013) reported a significant association between activation of the left inferior orbitofrontal cortex and hyperthymic temperament scores in healthy subjects in a functional magnetic resonance imaging (fMRI) investigation.

Recent meta-analyses of brain morphology in bipolar patients have shown reduction of regional gray matter volumes in the medial frontal gyrus including anterior cingulate cortex and bilateral fronto-insular cortex (Bora et al., 2010). In view of the putative association of affective temperaments with bipolar disorder, we have hypothesized that temperaments may be associated with the brain morphology. To the best of our knowledge, this potential association has not been investigated in healthy subjects without family history, and so the aim of the present study is to investigate whether cyclothymic and hyperthymic temperaments demonstrate associations with regional brain morphology in healthy subjects with neither history nor family history of psychiatric disorders.

2. Methods

2.1. Subjects

Sixty healthy Japanese subjects (30 males, 30 females) were recruited. The mean age of subjects was 26.7 (SD=5.63). All underwent screening for the past or present psychiatric disorder with the Mini-International Neuropsychiatric Interview (MINI). Based on the 17 items Hamilton Rating Scale for Depression (HAM-D) and Young Mania Rating Scale (YMRS), all were investigated regardless of whether they were in euthymic mood. The presence of psychiatric family history was also investigated by a question. All were right handed according to the Edinburgh handedness questionnaire. Magnetic Resonance Imaging (MRI) was not contraindicated in any subject. As gender effects in bipolar disorder have been reported (Jogia et al., 2012), the proportion of male and females was balanced and a factorial effect of gender was incorporated in the analyses. This study was approved by the ethical committee of Oita University Faculty of Medicine and a written informed consent was obtained from all subjects after explanation of this study.

2.2. Affective temperaments evaluation

The Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire (TEMPS-A) was used for bipolar temperament evaluation. TEMPS-A consists of 110 questions to measure 5 temperaments (depressive, cyclothymic, hyperthymic, irritable and anxious) and has been verified in 32 language versions and widely used in a number of epidemiological and clinical studies with psychiatric patients and healthy subjects. This scale has been developed by Akiskal and is widely used and confirmed to be reliable and valid internationally and in Japan (Akiskal et al., 2005; Goto et al., 2011; Sprooten et al., 2011; Serafini et al., 2011; Araki et al., 2012; Kohno et al., 2012). In the present study, subjects were divided into groups of high and low cyclothymic temperament by a cut-off of 4 points, and into high and low hyperthymic groups by a cut-off of 6 points. The cut-offs were determined from the mean scores of a non-clinical population of 1391 Japanese (Matsumoto et al., 2005).

2.3. MRI acquisition

Using a 3T MRI scanner (MAGNETOM Verio, Siemens, Erlangen, Germany), T1-weighted structural images were acquired for each subject with a 3-D magnetization prepared rapid gradient echo (MPRAGE) sequence in the sagittal plane (TR 2040 ms, TE 2.53 ms, TI 900 ms, the flip angle 9°, FOV 192 mm, and voxel size $1 \times 1 \times 1$ mm). We used a 32-channel coil for receiving RF. Total time for scanning was 4 min 28 s for each subject.

2.4. Image analysis

We used SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) which worked on Matlab 2012a for image analysis. We used VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm/download/) for preprocessing with the optimized voxel-based morphometry (VBM) (Good et al., 2001). Individual gray matter maps were normalized initially with a non-linear algorithm to the standard space of MNI152 brain. Then gray matter maps were averaged across subjects to generate a study-specific template, to which subjects' gray matter maps were spatially re-normalized non-linearly. Normalized gray matter maps were modulated by Jacobian determinants, and smoothed with an 8 mm FWHM Gaussian filter.

First, smoothed gray matter volumes (GMVs) were analyzed for the effects of temperament groups (high cyclothymic temperament group versus low cyclothymic temperament or high hyperthymic temperament group versus low hyperthymic temperament group) in a voxel-wise manner using General Linear Model (GLM). We investigated the main effects for temperament groups and gender, as well as for interaction of temperament groups and gender using GLM. We adapted age and total GMVs as covariates of no interest. Significance level was set to $p < 0.05$ with cluster-level multiple correction (Family-Wise Error; FWE corrected) and voxels with $p < 0.001$ (uncorrected) were identified within the significant cluster. Anatomical structures were defined with the Talairach Daemon Labels of WFU PickAtlas Tool (Maldjian et al., 2003).

Secondly, we performed a regions of interest (ROI) analysis to investigate regression between relative regional GMVs and cyclothymic or hyperthymic temperament score. The ROI was set at 10 mm diameter sphere, center of peak coordinate of the clusters, and the mean value within this ROI was obtained from each non-smoothed GMV image. Regional GMVs were calculated using get_totals.m custom Matlab code (http://www.cs.ucl.ac.uk/staff/G.Ridgway/vbm/get_totals.m) with ROI mask images, and relative regional GMVs were calculated by dividing by total GMVs and further multiplied by 100. The regression significance between relative regional GMVs and cyclothymic or hyperthymic temperament scores was analyzed using GLM. We then analyzed again for the effect of gender using ANCOVA.

We also evaluated the effect of both bipolar temperaments (subjects belonging to both high cyclothymic group and high hyperthymic group versus the others). Finally, ROI analyses were conducted as above to evaluate regression of relative regional GMVs across temperament scores. Statistics in ROI analysis were performed by IBM SPSS Statistics Version 21.

3. Results

3.1. Demographic data

All subjects had neither past nor present psychiatric illness. Moreover, they had no family psychiatric history. The mean score (SD) of HAM-D was 1.44 (1.88) and that of YMRS was 0.91 (0.87) and all subjects were determined to be in euthymic mood. The mean scores (SD) of cyclothymic and hyperthymic temperaments

Table 1
Demographic data by gender.

	Male ($n=30$)[a]	Female ($n=30$)[a]	p
Age (years)	27.6 (5.95)	25.8 (4.99)	0.218
HAM-D scores	1.30 (1.84)	1.57 (2.16)	0.609
YMRS scores	0.93 (0.94)	0.57 (0.97)	0.144
Cyclothymic scores[b]	4.20 (3.80)	4.37 (3.23)	0.855
Hyperthymic scores[b]	5.30 (4.32)	4.37 (3.81)	0.378

HAM-D=the 17 items Hamilton Rating Scale for Depression and YMRS=Young Mania Rating Scale.

[a] The data were presented as mean (SD).

[b] The temperament scores were evaluated by the Temperament Scale of Memphis, Pisa, Paris and San Diego-Autoquestionnaire.

as measured by TEMPS-A were 4.28 (3.50) and 4.85 (4.05), respectively. High and low cyclothymic groups consisted of 29 and 31 subjects respectively while high and low hyperthymic groups were 20 and 40 subjects each. Moreover, 12 subjects belonged to both high cyclothymic and high hyperthymic groups. The mean values of TEMPS-A were not significantly different from those of the validation sample ($n=1391$) of non-clinical Japanese population (cyclothymic temperament: $T_{1449}=0.28$, $p=0.78$; hyperthymic temperament: $T_{1449}=0.71$, $p=0.47$) (Matsumoto et al., 2005). No significant correlation was found between cyclothymic and hyperthymic temperaments, which was also consistent with the results of the larger sample (Matsumoto et al., 2005). As shown in Table 1, there was no significant difference in the values of HAM-D, YMRS, cyclothymic or hyperthymic temperament scores between genders.

3.2. Regional GMVs—effect of affective temperaments

First, we examined cyclothymic group effects (i.e., high and low cyclothymic groups) on the regional GMVs and found a significant cluster (Table 2 and Fig. 1A), which was located in the left medial frontal gyrus (MFG) containing 666 voxels with a local maxima of $Z=4.73$, located at x, y,and $z=-12$, 46, and 20, respectively in MNI space. There was no interaction effect between cyclothymic temperament scores and gender. Moreover, cyclothymic temperament scores had a significant correlation with relative regional GMVs in the left MFG ($R^2=0.156$, $F_{1,58}=10.734$, and $p=0.002$, Fig. 1B) whereas there was no significant interaction effect between cyclothymic temperament scores and gender ($F_{9,36}=0.667$, $p=0.733$).

Secondly, despite the absence of main effect in the hyperthymic groups, a significant effect of interaction between gender and hyperthymic groups was present (Table 2 and Fig. 2A), which was again located in the left MFG with 794 voxels cluster size and a local maxima of $Z=4.96$, located at x, y, and $z=-12$, 40, and 27, respectively in MNI space. Post-hoc t-test analysis showed that GMVs of left MFG were significantly larger in male subjects of the high hyperthymic group compared to males of the low hyperthymic group (Table 2) whereas no significant clusters were found in female group. Hyperthymic temperament scores significantly predicted relative regional GMVs in the left MFG ($R^2=0.084$, $F_{1,58}=5.350$, and $p=0.024$, Fig. 2B). Moreover, there was a significant interaction between gender and hyperthymic temperament scores for relative regional GMVs in the left MFG ($F_{10,33}=3.501$, $p=0.003$, Fig. 2C).

Finally, additional analysis for subjects belonging to both high cyclothymic temperament and high hyperthymic temperament groups showed a significantly larger regional GMV again in the left MFG compared to the remaining subjects (Table 2 and Fig. 3). Relative regional GMV of ROI at the peak of this cluster in the left MFG was significantly predicted by both cyclothymic score ($\beta=0.258$, $p=0.040$) and hyperthymic score ($\beta=0.289$, $p=0.022$) in the multiple regression analysis.

Furthermore, we performed similar analyses for other three affective temperaments (depressive, irritable and anxious temperaments), but no significant difference of regional gray matter volume was observed.

4. Discussion

To the best of our knowledge, this is the first study to investigate the association between affective temperaments and regional brain volume in healthy subjects without an apparent psychiatric family history. The present findings suggest that cyclothymic and hyperthymic temperaments may be associated with the gray matter volume of the left MFG.

The MFG seems to be involved in a neural process linking emotion and cognitive functions (Ridderinkhof et al., 2004; Dolcos et al., 2004; Stone et al., 1998; Rubino et al., 2007; Koechlin et al., 2000; Lotze et al., 2007). This region may be a functional junction connected to the ventral lateral prefrontal cortex and limbic systems such as the amygdala, insula and frontoparietal networks (Liu et al., 2012; Chai et al., 2011).

Several lines of evidence suggest that abnormal activity of the MFG is critical in bipolar disorder. Abnormality of the MFG in bipolar patients has been reported in studies conducting both emotional and cognitive tasks (Lawrence et al., 2004; Malhi et al., 2005; Agarwal et al., 2010; Chen et al., 2011; Matsuo et al., 2012). A meta-analysis of fMRI studies of individuals who had genetic risk for bipolar disorder has found that an increased neural response exists in the MFG as well as the left superior frontal gyrus and left insula (Fusar-Poli et al., 2012). In the consensus model of functional neuroanatomy of bipolar disorders, it was hypothesized that disruption in early development within brain networks that modulate emotional behavior leads to decreased connectivity among ventral prefrontal networks and limbic brain regions, especially the amygdala, and ventromedial prefrontal cortex including the MFG has been engaged in internal emotional control (Strakowski et al., 2012). Therefore, the potential relationship between bipolar temperaments and bipolar disorder via the MFG may be underscored by our findings in a non-clinical population.

Volume reduction in the left MFG in bipolar disorder has been consistently reported (Bora et al., 2010; Ellison-Wright and Bullmore, 2010; Rimol et al., 2010). In this study, we found regional GMVs in the left MFG positively predicted cyclothymic and/or hyperthymic temperaments, but the increased changes were in the opposite direction to those of patients with bipolar disorder whose volumes were reported to be decreased when compared to controls. Without longitudinal data, it is uncertain when the apparent increase of the left MFG occurred and whether it was genetically determined and/or acquired. Nonetheless, common factors between cyclothymic and hyperthymic temperaments are implicated in the volume increase because the volumes of the subjects with both high bipolar temperaments were significantly larger than the others. Although it is presently unknown if temperaments themselves and/or relevant common factors directly increase the volume of the left MFG, one possibility is that increased volume may be associated with high energy level and emotional intensity in individuals with hyperthymic temperament and mood instability and emotional instability in those with cyclothymic temperament, respectively. At a certain point, a catastrophic change may happen and a subsequent pathological process decreases the volume of the MFG corresponding to the onset and the course of bipolar disorder, which remains yet to be determined. In addition to these pathological processes, normal

Table 2
Significant clusters in voxel-based morphometry analysis for the effect of affective temperaments.

Region[a]	p[b]	Number of voxels in cluster	Z value	Coordinate of local maxima (x, y, z) in MNI space
Main effect of cyclothymic temperament group				
Left medial frontal gyrus	0.023	666	4.73	−12, 46, 20
Interaction effect between hyperthymic temperament group and gender				
Left medial frontal gyrus	0.011	794	4.96	−12, 40, 27
Contrast of group difference between subjects with high and low hyperthymic temperament in male				
Left medial frontal gyrus	0.005	832	4.82	−12, 41, 30
Contrast of group difference for subjects with both high cyclothymic and high hyperthymic temperament versus *the others*				
Left medial frontal gyrus	0.039	582	3.91	−12, 38, 33

MNI = Montreal Neurological Institute and FEW = Family-Wise Error.

[a] Regions were labeled by *Tarairach daemon* of wfu pickatlas.
[b] FWE corrected $p < 0.05$.

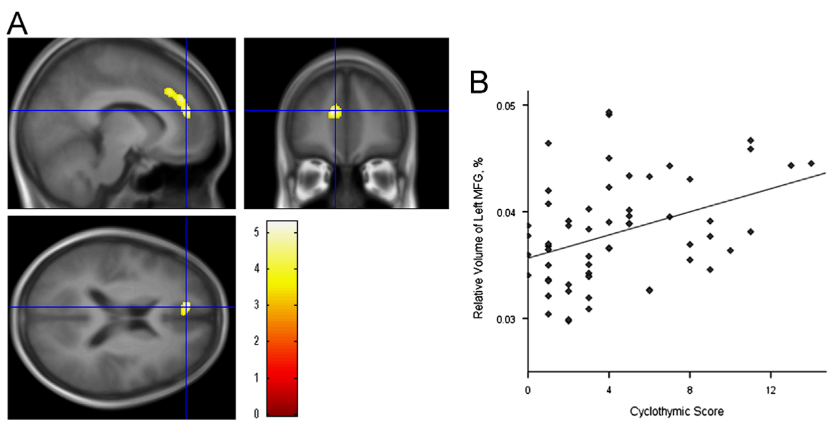

Fig. 1. Effect of cyclothymic temperament on regional gray matter. (A) A significant cluster which had the main effect of cyclothymic group was significant at $p < 0.05$ (family-wise error corrected). A color bar shows T value. (B) Relative regional gray matter volumes (GMVs) in the left medial frontal gyrus (MFG) was significantly predicted by cyclothymic scores ($R^2 = 0.156$, $F_{1,58} = 10.734$, and $p = 0.002$).

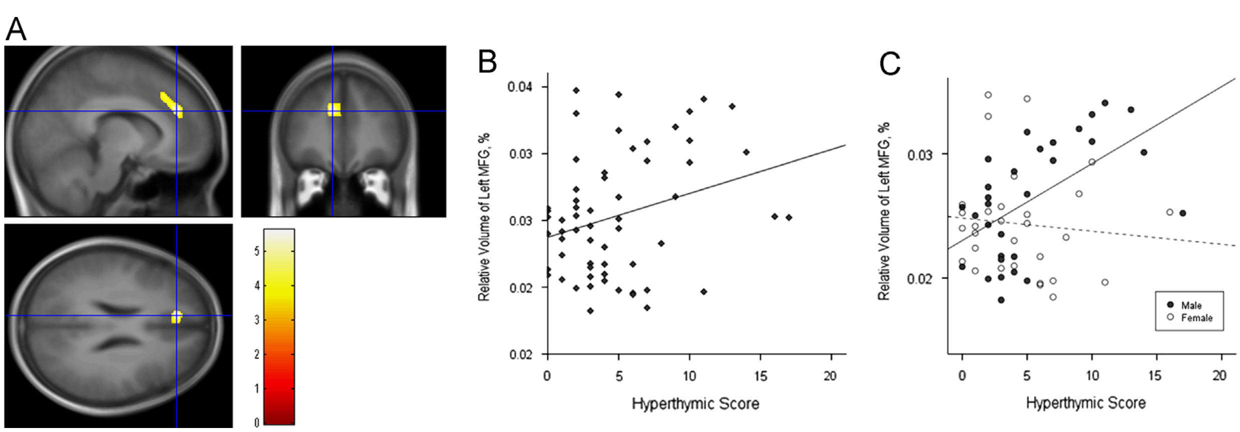

Fig. 2. Effect of hyperthymic temperament on regional gray matter. (A) A significant cluster which had interaction effect between hyperthymic group and gender was significant at $p < 0.05$ (family-wise error corrected). A color bar shows T value. (B) Relative regional gray matter volumes (GMVs) in the left medial frontal gyrus (MFG) was significantly predicted by hyperthymic scores ($R^2 = 0.084$, $F_{1,58} = 5.350$, and $p = 0.024$). (C) Regression between relative regional GMVs in left medial frontal gyrus (MFG) and hyperthymic temperament by gender. Interaction effect between hyperthymic temperament scores and gender was statistically significant ($F_{10,33} = 3.501$, and $p = 0.003$).

process such as aging (Lemaitre et al., 2012), learning and training (Draganski et al., 2004; Scholz et al., 2009; Zatorre et al., 2012) may also affect the volume.

The present study has some limitations. The subjects were relatively young and the number was relatively small, limiting the generalizability of our findings. Furthermore, due to the nature of a cross-sectional research design we could not determine the causal relationship between temperament and the volume changes. Finally, the operationalization of the 'high and low' temperament was arbitrary. Therefore, we added a dimensional approach, which reconfirmed the validity of our findings. Conversely, our study also has considerable strengths. We used strict criteria for normal healthy subjects excluding any psychiatric illnesses, and adjusted subjects with gender and age, which might have correctly determined the effects of temperaments on the brain volume.

In conclusion, whilst more remains to be elucidated about the neural substrates of temperament, the present findings suggest

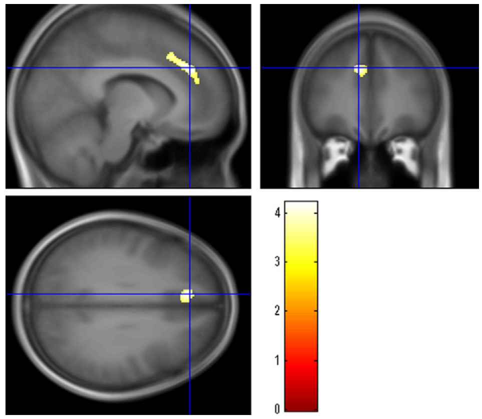

Fig. 3. Effect of both cyclothymic and hyperthymic temperament on the regional gray matter. A significant cluster which had larger volume in subjects with both high cyclothymic and high hyperthymic temperaments than the others which was significant at $p < 0.05$ (family-wise error corrected). A color bar shows T value.

that cyclothymic and hyperthymic temperaments may have their morphological basis in the left MFG in healthy subjects.

Role of funding source

This work was supported by Grant-in-Aid for Scientific Research (C) (24591723) from the Japanese Society for the Promotion of Science.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgments

We greatly appreciate Dr. Tsuyoshi Akiyama for his permission of the use of The Japanese version of TEMPS-A.

References

Agarwal, N., Port, J.D., Bazzocchi, M., Renshaw, P.F., 2010. Update on the use of MR for assessment and diagnosis of psychiatric diseases1. Radiology 255, 23–41.
Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D., 2005. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J. Affect. Disord. 85, 3–16.
Akiskal, H.S., Pinto, O., 1999. The evolving bipolar spectrum: prototypes I, II, III, and IV. Psychiatr. Clin. North Am. 22, 517–534.
Alloy, L.B., Urosevic, S., Abramson, L.Y., Jager-Hyman, S., Nusslock, R., Whitehouse, W.G., Hogan, M., 2012. Progression along the bipolar spectrum: a longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II Disorders. J. Abnorm. Psychol. 121, 16–27.
Araki, Y., Terao, T., Hoaki, N., Wang, Y., Goto, S., 2012. Bipolar temperaments and light. J. Affect. Disord. 136, 740–742.
Bora, E., Fornito, A., Yücel, M., Pantelis, C., 2010. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. Biol. Psychiatry 67, 1097–1105.
Chai, X.J., Whitfield-Gabrieli, S., Shinn, A.K., Gabrieli, J.D.E., Nieto Castañón, A., McCarthy, J.M., Cohen, B.M., Öngür, D., 2011. Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. Neuropsychopharmacology 36, 2009–2017.
Chen, C.-H., Suckling, J., Lennox, B.R., Ooi, C., Bullmore, E.T., 2011. A quantitative meta-analysis of fMRI studies in bipolar disorder. Bipolar Disord. 13, 1–15.
Dolcos, F., LaBar, K.S., Cabeza, R., 2004. Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. Neuroimage 23, 64–74.
Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., May, A., 2004. Neuroplasticity: changes in grey matter induced by training. Nature 427, 311–312.
Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr. Res. 117, 1–12.
Fusar-Poli, P., Howes, O., Bechdolf, A., Borgwardt, S., 2012. Mapping vulnerability to bipolar disorder: a systematic review and meta-analysis of neuroimaging studies. J. Psychiatry Neurosci. Jpn. 37, 170–184.
Ghaemi, S.N., Ko, J.Y., Goodwin, F.K., 2001. The bipolar spectrum and the antidepressant view of the world. J. Psychiatr. Pract. 7, 287–297.
Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N.A., Friston, K.J., Frackowiak, R.S.J., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 14, 21–36.
Goto, S., Terao, T., Hoaki, N., Wang, Y., 2011. Cyclothymic and hyperthymic temperaments may predict bipolarity in major depressive disorder: a supportive evidence for bipolar II1/2 and IV. J. Affect. Disord. 129, 34–38.
Harada, M., Hoaki, N., Terao, T., Hatano, K., Kohno, K., Araki, Y., Mizokami, Y., Kodama, K., Toyokawa, K., Izumi, T., Arasaki, M., Shimomura, T., Fujiki, M., Kochiyama, T., 2013. Hyperthymic temperament and brightness judgment in healthy subjects: involvement of left inferior orbitofrontal cortex. J. Affect. Disord. 151, 143–148.
Harnic, D., Pompili, M., Mazza, M., Innamorati, M., Di Nicola, M., Catalano, V., Bruschi, A., Del Bono, D., Forte, A., Lester, D., Girardi, P., Bria, P., Janiri, L., 2013. Affective temperaments and psychopathological dimensions of personality in bipolar and cyclothymic patients. Behav. Med. (Washington, DC) 39, 17–23.
Jogia, J., Dima, D., Frangou, S., 2012. Sex differences in bipolar disorder: a review of neuroimaging findings and new evidence. Bipolar Disord. 14, 461–471.
Koechlin, E., Corrado, G., Pietrini, P., Grafman, J., 2000. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proc. Natl. Acad. Sci. 97, 7651–7656.
Kohno, K., Hoaki, N., Inoue, T., Nakai, Y., Toyomaki, A., Araki, Y., Hatano, K., Terao, T., 2012. Latitude effect on bipolar temperaments. J. Affect. Disord. 142, 53–56.
Lawrence, N.S., Williams, A.M., Surguladze, S., Giampietro, V., Brammer, M.J., Andrew, C., Frangou, S., Ecker, C., Phillips, M.L., 2004. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol. Psychiatry 55, 578–587.
Lemaitre, H., Goldman, A.L., Sambataro, F., Verchinski, B.A., Meyer-Lindenberg, A., Weinberger, D.R., Mattay, V.S., 2012. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? Neurobiol. Aging 33, 617.e1–617.e9.
Liu, C.-H., Ma, X., Li, F., Wang, Y.-J., Tie, C.-L., Li, S.-F., Chen, T.-L., Fan, T., Zhang, Y., Dong, J., Yao, L., Wu, X., Wang, C.-Y., 2012. Regional homogeneity within the default mode network in bipolar depression: a resting-state functional magnetic resonance imaging study. Plos One 7, e48181.
Lotze, M., Veit, R., Anders, S., Birbaumer, N., 2007. Evidence for a different role of the ventral and dorsal medial prefrontal cortex for social reactive aggression: an interactive fMRI study. NeuroImage 34, 470–478.
Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19, 1233–1239.
Malhi, G.S., Lagopoulos, J., Sachdev, P.S., Ivanovski, B., Shnier, R., 2005. An emotional Stroop functional MRI study of euthymic bipolar disorder. Bipolar Disord. 7, 58–69.
Matsumoto, S., Akiyama, T., Tsuda, H., Miyake, Y., Kawamura, Y., Noda, T., Akiskal, K. K., Akiskal, H.S., 2005. Reliability and validity of TEMPS-A in a Japanese non-clinical population: application to unipolar and bipolar depressives. J. Affect. Disord. 85, 85–92.
Matsuo, K., Kopecek, M., Nicoletti, M.A., Hatch, J.P., Watanabe, Y., Nery, F.G., Zunta-Soares, G., Soares, J.C., 2012. New structural brain imaging endophenotype in bipolar disorder. Mol. Psychiatry 17, 412–420.
Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., Nieuwenhuis, S., 2004. The role of the medial frontal cortex in cognitive control. Science 306, 443–447.
Rimol, L.M., Hartberg, C.B., Nesvåg, R., Fennema-Notestine, C., Hagler Jr., D.J., Pung, C.J., Jennings, R.G., Haukvik, U.K., Lange, E., Nakstad, P.H., Melle, I., Andreassen, O.A., Dale, A.M., Agartz, I., 2010. Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. Biol. Psychiatry 68, 41–50.
Rovai, L., Maremmani, A.G.I., Rugani, F., Bacciardi, S., Pacini, M., Dell'osso, L., Akiskal, H.S., Maremmani, I., 2013. Do Akiskal & Mallya's affective temperaments belong to the domain of pathology or to that of normality? Eur. Rev. Med. Pharmacol. Sci. 17, 2065–2079.
Rubino, V., Blasi, G., Latorre, V., Fazio, L., d' Errico, I., Mazzola, V., Caforio, G., Nardini, M., Popolizio, T., Hariri, A., Arciero, G., Bertolino, A., 2007. Activity in medial prefrontal cortex during cognitive evaluation of threatening stimuli as a function of personality style. Brain Res. Bull. 74, 250–257.
Scholz, J., Klein, M.C., Behrens, T.E.J., Johansen-Berg, H., 2009. Training induces changes in white-matter architecture. Nat. Neurosci. 12, 1370–1371.
Serafini, G., Pompili, M., Innamorati, M., Fusar-Poli, P., Akiskal, H.S., Rihmer, Z., Lester, D., Romano, A., de Oliveira, I.R., Strusi, L., Ferracuti, S., Girardi, P., Tatarelli, R., 2011. Affective temperamental profiles are associated with white matter hyperintensity and suicidal risk in patients with mood disorders. J. Affect. Disord. 129, 47–55.
Sprooten, E., Sussmann, J.E., Clugston, A., Peel, A., McKirdy, J., Moorhead, T.W.J., Anderson, S., Shand, A.J., Giles, S., Bastin, M.E., Hall, J., Johnstone, E.C., Lawrie, S. M., McIntosh, A.M., 2011. White matter integrity in individuals at high genetic risk of bipolar disorder. Biol. Psychiatry 70, 350–356.
Stone, V.E., Baron-Cohen, S., Knight, R.T., 1998. Frontal Lobe Contributions to Theory of Mind. J. Cogn. Neurosci. 10, 640–656.
Strakowski, S.M., Adler, C.M., Almeida, J., Altshuler, L.L., Blumberg, H.P., Chang, K.D., DelBello, M.P., Frangou, S., McIntosh, A., Phillips, M.L., Sussman, J.E., Townsend, J.D., 2012. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord. 14, 313–325.
Takeshima, M., Oka, T., 2013. A comprehensive analysis of features that suggest bipolarity in patients with a major depressive episode: which is the best combination to predict soft bipolarity diagnosis? J. Affect. Disord. 147, 150–155.
Terao, T., 2012. Bipolar spectrum: Relevant psychological and biological factors. World J. Psychiatry 2, 71.
Zatorre, R.J., Fields, R.D., Johansen-Berg, H., 2012. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat. Neurosci. 15, 528–536.