Association Between Cortical Thickness or Surface Area and Divergent Thinking in Patients with Bipolar Disorder

Pei-Chi Tu[1,2,3,4]*, Wan-Chen Chang[1,2,5], Yi-Hsuan Kuan[6], Mu-Hong Chen[2,3,6], Tung-Ping Su[3,6,7]*

[1]Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
[2]Department of Psychiatry, Taipei Veterans General Hospital, Taipei 112, Taiwan
[3]Department of Psychiatry, Faculty of Medicine, National Yang-Ming Chiao Tung University, Taipei, Taiwan
[4]Institute of Philosophy of Mind and Cognition, National Yang Ming Chiao Tung University, Taipei, Taiwan
[5]Department of Biomedical Engineering, National Yang Ming Chiao Tung University, Taipei, Taiwan
[6]Institute of Brain Science, National Yang Ming Chiao Tung University, Taipei, Taiwan
[7]Department of Psychiatry, Department of Psychiatry, Cheng-Hsin General Hospital, Taipei, Taiwan

*__Correspondence:__ Tung-Ping Su, M.D., Chair, Department of Psychiatry, Cheng-Hsin General Hospital, No.45, Cheng Hsin St., Taipei 112, Taiwan, E-mail address: tomsu0402@gmail.com, Pei-Chi Tu, M.D. Ph.D., Department of Medical Research, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, Taipei, Taiwan, E-mail address: peichitu@gmail.com

Running title: Bipolar Disorder and Divergent Thinking: SBM

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Abstract

Objective:

Divergent thinking is a critical creative cognitive process. Its neural mechanisms have been well-studied through structural and functional imaging in healthy individuals but are less explored in patients with bipolar disorder (BD). Because of the traditional link between creativity and BD, this study investigated the structural correlates of divergent thinking in patients with BD through surface-based morphometry.

Methods:

Fifty-nine patients diagnosed with BD I or BD II (35.3 ± 8.5 years) and 56 age- and sex-matched controls (33.9 ± 7.4 years) were recruited. The participants underwent structural magnetic resonance imaging and an evaluation of divergent thinking by using the Chinese version of the Abbreviated Torrance Test for Adults (ATTA). FreeSurfer 7.0 was used to generate thickness and surface area maps for each participant. Brainwise regression of the association between cortical thickness or surface area and ATTA performance was conducted using general linear models.

Results:

Divergent thinking performance did not differ significantly between the patients with BD and the healthy controls. In these patients, total ATTA score was negatively correlated with cortical thickness in the right middle frontal gyrus, right occipital, and left precuneus but positively correlated with the surface area of the right superior frontal gyrus. By contrast, total ATTA scores and cortical thickness or surface area were not significantly correlated among the controls.

Conclusion:

The findings indicate that divergent thinking involves cerebral structures for executive control, mental imagery, and visual processing in patients with BD, and the right prefrontal cortex might be the most crucial of these structures.

Keywords: bipolar disorder, divergent thinking, cortical thickness, prefrontal cortex, MRI

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Introduction

Bipolar disorder (BD) is a major psychiatric disorder characterized by the fluctuation of mood states and social function impairment. Although prominent cognitive impairment has been identified in patients with BD, evidence exists of a link between BD and creativity. Individuals in creative professions are more to have BD than are controls (Kyaga et al., 2013), and individuals with BD and their healthy first-degree relatives exhibit higher overall creative achievement than do healthy individuals (Richards, Kinney, Lunde, Benet, & Merzel, 1988). One study of 1558 participants found that a higher BD polygenic risk score was associated with not only increased divergent thinking performance but also higher gray matter volumes in the right inferior frontal gyrus (Takeuchi et al., 2021). The aforementioned study suggested that genetic risk factors for BD also contributed to superior performance in divergent thinking and an increase in related cortical changes. Nevertheless, the results of studies evaluating the performance of noneminent creativity in patients with BD are less consistent, and results might depend on the measurements used in the experiments (Santosa et al., 2007).

One key measurement of creative cognitive processes is divergent thinking, which refers to the process of extrapolating many possible responses to an initial stimulus or data. Several functional magnetic resonance imaging (fMRI) studies have demonstrated that the posterior midline structures, including the precuneus or cuneus and posterior cingulate cortex, are critical for mental imagery and might also be important for divergent thinking (Cavanna & Trimble, 2006) (Mayseless, Eran, & Shamay-Tsoory, 2015). Furthermore, a meta-analysis of fMRI studies found that divergent thinking activates a distributed network, including the lateral prefrontal cortex, posterior parietal cortex, precuneus, anterior cingulate cortex, left middle temporal gyrus, and left fusiform gyrus (Wu et al., 2015). These functional studies indicate that divergent thinking might involve multiple cognitive process, including visual processing, verbal processing, mental imagery, and executive control.

The neural substrates for divergent thinking have also been revealed by evaluating the association between divergent thinking performance and cortical structures. In healthy individuals, several studies utilizing voxel-based morphometry (VBM) have delineated a correlation between performance in divergent thinking tasks and gray matter volume, employing diverse metrics of divergent thinking. One investigation, employing the verbal imagination subscales of the Berliner Intelligenz-Struktur-Test, revealed a significant positive relationship between verbal creativity and gray matter density in the right cuneus and right precuneus (Fink et al., 2014). Another study, conducted by Jauk et al. (2015), employed six distinct divergent thinking tasks, comprising three alternate uses (AU) tasks and three

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

instances (IN) tasks, unveiling an association between ideational originality and gray matter volume in the precuneus and caudate nucleus (Jauk et al., 2015). Additionally, a study utilizing the S-A creativity test (Minds, 1969) detected positive correlations between individual creativity and regional gray matter volume in the right dorsolateral prefrontal cortex, bilateral striatum, substantia nigra, tegmental ventral area, and periaqueductal gray (Takeuchi et al., 2010). Moreover, another investigation employing the verbal version of the Torrance Tests of Creative Thinking found a significant positive correlation between verbal creativity and regional gray matter volume in the bilateral inferior frontal gyrus (Zhu et al., 2013). Several surface-based morphometry (SBM) studies have demonstrated further association between divergent thinking performance and cortical thickness or surface area. One study demonstrated that divergent thinking measured using the composite creativity index was negatively correlated with cortical thickness within the lingual gyrus and positively correlated with cortical thickness in the right posterior cingulate (Jung et al., 2010). Another study of 310 healthy adults found that visual creativity was significantly negatively correlated with cortical thickness in the left middle frontal gyrus, right inferior frontal gyrus, right supplementary motor cortex, and left insula (Tian et al., 2018). The aforementioned VBM and SBM studies support the importance of distributed neural substrates, including the cuneus, precuneus, and prefrontal regions, in the neural processing of divergent thinking in healthy individuals.

Few functional and structural studies have been conducted on divergent thinking in patients with BD, and whether patients with BD and healthy individuals share similar neural networks for creative thinking is unclear. Our VBM study found that divergent thinking performance was positively correlated with the gray matter volume of the dorsal part of the right medial prefrontal cortex (Brodmann area 9) in patients with BD, and the study emphasized the importance of cognitive control in creative thinking (Tu, Kuan, Li, & Su, 2017). The present study used SBM to investigate the association between divergent thinking performance and cortical thickness or surface area in patients with BD. Cortical thickness and surface area are two independent properties of gray matter and might contribute differently to individual differences in behavior, as demonstrated in a previous study (Kubera et al., 2018). We undertook the same analysis of a group of healthy controls (HCs) to understand whether patients with BD and HCs shared the same structural correlates of creative thinking. In the present investigation, we implemented a verbal test designed to assess divergent thinking, the outcomes of which have previously been linked with the prefrontal cortex in extant literature. Consequently, our hypothesis posits that there exists an association between the performance

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

on divergent thinking tasks and the cortical thickness or surface area of the prefrontal cortex among individuals diagnosed BD. Furthermore, we anticipate observing differential patterns of structural association between divergent thinking and brain morphology among HCs as revealed by our VBM analysis.

Materials and Methods

Participants

The BD group comprised 59 outpatients with a diagnosis of BD I or BD II from the Taipei Veterans General Hospital in Taiwan (Table 1). Diagnoses were confirmed through structured clinical interviews according to the *Diagnostic and Statistical Manual of Mental Disorders fourth edition* (DSM-IV) (First, Spitzer, Gibbon, & Williams, 1997). Participants were screened to exclude those with a history of head injury resulting in a sustained loss of consciousness or cognitive sequelae, neurological illness, or any disorder affecting cerebral metabolism. Mood symptom severity was evaluated by the 17-item Hamilton Depression Rating Scale (HDR-17) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). Patients meeting the criteria for euthymic state, defined by a score of <7 on the HDR-17 and a score of <7 on the YMRS, were enrolled. The patients were receiving treatment with various atypical antipsychotics, antidepressants, antiepileptics and lithium before participation in the experiment (Table 1). Fifty-six age-, sex-, and handedness-matched HCs were recruited through advertisement. These participants were screened using the Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998). In addition, those with first-degree relatives with Axis I disorders, including schizophrenia, major depression, or BD, were excluded. A total of 131 participants were initially enrolled in the study, comprising 65 individuals diagnosed with BD and 66 HCs. Subsequently, 16 participants were excluded due to failure to meet the research criteria, incomplete evaluation processes, or insufficient image quality. Consequently, the final cohort for data analysis comprised 59 patients with BD and 56 HCs (detailed enrollment process in supplementary figure 1). All procedures were approved by the Institutional Review Board of the Taipei Veterans General Hospital, and all participants provided written informed consent after they were apprised of the experimental procedures.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Measurement of divergent thinking

We adopted the Chinese version of the Abbreviated Torrance Test for Adults (ATTA) (Goff & Torrance, 2002), which was edited by C. Y. Chen (2006), for evaluating divergent thinking. The test includes one verbal and two figural responses. During the test, participants were encouraged to devise novel responses to verbal or figurative stimuli. The four norm-referenced measures were as follows: (1) fluency—the ability to produce quantities of ideas relevant to the task instruction; (2) originality—the ability to produce uncommon ideas or ideas that are completely new or unique; (3) elaboration—the ability to embellish ideas with details; and (4) flexibility— the ability to process information or objects in different ways when provided the same stimulus. We used the creativity index, which was calculated from the 4 norm-referenced measures and 15 criterion-referenced creativity indicators, to conduct our main regression in this study.

Image acquisition

Images were acquired using a whole-body, high-speed magnetic resonance imaging system (3.0T GE Discovery MR750). Head stabilization was achieved with cushioning, and all participants wore earplugs (29-dB rating) to attenuate any noise. A high-resolution structural image was acquired in the sagittal plane by using a high-resolution sequence (repetition time [TR] = 8.38 ms, echo time [TE] = 3.54 ms, inversion time [TI] = 450 ms and flip angle = 12°) and an isotropic 1-mm voxel (field of view = 256 × 256).

Analysis of cortical thickness and surface area

All structural T1 images were analyzed using FreeSurfer (version 7.0, www.nmr.mgh.harvard.edu/martinos) to create anatomical surface models and for statistical analyses (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). For each participant, the processing stream included the removal of nonbrain tissue, transformation to Talairach space, and segmentation of gray–white matter tissue. The thickness measurements across the cortex were computed by determining the point on the gray–white matter boundary surface closest to a given point on the estimated pial surface (and vice versa) and averaging these two values (Fischl & Dale, 2000). The accuracy of the thickness measurements derived using this technique has been validated using histological (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003). To map each participant to a common space, the surface representing the gray–white matter boundary was registered to an average cortical surface atlas by using a nonlinear procedure that optimally aligned sulcal and gyral features among the participants (Fischl, Sereno, & Dale, 1999). For vertex-by-vertex cluster analysis,

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

the thickness or surface area maps of all participants in both groups were converted to a common atlas space (Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999). The data were smoothed by applying a two-dimensional Gaussian smoothing kernel with a size of 10 mm. With regard to quality control of MRI images and cortical segmentations, we adopted the strategy of visual inspection with exclusion that excluded images with artifacts or segmentation failures. In this study, the MRI images of 116 participants (60 patients with BD and 56 HCs) were evaluated and the images of one patient with BD were excluded due to quality control.

Statistical analyses

We employed the qdec (Query, Design, Estimate, Contrast) analysis tool integrated within the Freesurfer software to perform group-level statistical analyses. This tool provides researchers with a robust platform for investigating brain morphometric differences associated with diverse experimental factors and clinical conditions using structural MRI data within the Freesurfer environment. Our main analysis investigated the structural correlates of divergent thinking in patients with BD. A general linear model was used to analyze the correlation between cortical thickness or surface area and ATTA scores by using age, education, and intracranial volume as covariates of no interest. We used an uncorrected threshold of $p < .01$ for initial vertex-wise comparisons. To correct for multiple comparisons, Monte Carlo simulations were performed 10 000 times. At the cluster level, only clusters with a significance of $p < .05$ were reported. The correlation between divergent thinking and cortical thickness or surface area was analyzed separately for the patients with BD and the HCs in the main analysis. We also performed a supplementary analysis of the correlations of the four norm-referenced measures of fluency, elaboration, originality, and flexibility with cortical thickness or surface area to understand whether different components of divergent thinking involved different cortical structures.

Results

The demographic and behavioral data of the participants are presented in Table 1. The total ATTA scores and the ATTA scores for the four norm-referenced measures did not differ significantly between the patients with BD and the HCs.

In the patients with BD, ATTA score correlated negatively with the cortical thicknesses of the right middle frontal, right lateral occipital, and left precuneus (Figure 1, Table 2). By contrast, ATTA score correlated positively with the surface area of the right superior frontal

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

gyrus (Figure 2, Table 2). In the HCs, ATTA score did not correlate significantly with cortical thickness or surface area. In the study, evaluations of ATTA were conducted prior to image acquisition within the same week, with an average interval of 4 days.

We conducted supplementary analysis of the associations of the four norm-referenced measures with cortical thickness or surface area. In the patients with BD, these measures correlated negatively with cortical thickness in different cortical structures (Figure 1, Table 2). The cortical thickness of the right rostral middle frontal gyrus correlated with originality, whereas that of the right lateral occipital cortex correlated with fluency. The surface area of the right superior frontal gyrus also correlated positively with elaboration, flexibility, and originality (Figure 2, Table 2). In the HCs, originality and the cortical thicknesses of the right inferior frontal, occipital, and left insula were positively correlated (Figure 1, Table 2).

In the patients with BD, we conducted further analysis to clarify the effects of psychosis history, BD subtype (I vs. II), age of onset, and illness duration on total ATTA score and the cortical thicknesses of the structures listed in Table 2. The results demonstrated that only illness duration exerted significant effects on total ATTA score and cortical thickness. Patients with BD with long illness duration exhibited significantly lower cortical thickness in the right lateral occipital cortex ($t = 2.34$, $p = .02$) than did patients with short illness duration; however, ATTA scores did not differ significantly between these two groups.

Additionally, we conducted between-group analyses examining cortical thickness and surface area difference between patients with BD and HCs utilizing a general linear model. Covariates including age, gender, education, and intracranial volume were included as covariates of no interest. The findings revealed a significant decrease in cortical thickness within the left inferior temporal gyrus among BD patients compared to HCs (supplementary Figure 2). Conversely, no significant differences in cortical surface area were evident between the two cohorts.

Discussion

This study used SBM to evaluate the association between divergent thinking performance and cortical thickness or surface area in patients with BD and identified that higher ATTA scores were associated with lower cortical thicknesses in the right rostral middle frontal gyrus, right occipital, and left precuneus but with a larger surface area in the right superior frontal gyrus. These findings suggest that divergent thinking involves the interaction of multiple networks for visual processing (occipital), mental image generation (precuneus), and executive control (prefrontal cortex). Because the correlations between

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

cortical structure and behavioral performance were limited in our sample of HCs, the structural change in the pathogenesis of patients with BD might cause additional variation and be helpful in elucidating the neural process underlying divergent thinking.

The most significant correlation and largest cluster was obtained for the right rostral middle frontal gyrus. The right middle frontal gyrus is a key node of the executive control network, and our findings indicate that executive control might have a critical influence on divergent thinking performance in patients with BD. Studies have also provided evidence of the importance of the prefrontal cortex in creative thinking. The activation of the dorsolateral prefrontal cortex has been consistently demonstrated during divergent thinking tasks in two meta-analyses of fMRI studies (Wu et al., 2015) (Cogdell-Brooke, Sowden, Violante, & Thompson, 2020). Furthermore, one study observed functional changes in the dorsolateral prefrontal cortex caused by training in divergent thinking and suggested that the enhancement of creativity might rely not only on the posterior brain but also on areas involved in top-down cognitive control (Sun et al., 2016). However, the relationship between prefrontal function and creativity might not be straightforward. For example, frontal damage caused by focal lesions or neurodegenerative diseases is associated with impairments in various creativity tasks. However, paradoxically, a series of clinical observations reported the facilitation of artistic production in patients with neurodegenerative diseases affecting the prefrontal cortex, such as frontotemporal dementia (de Souza et al., 2014). Therefore, a complex relationship between prefrontal function and creativity might exist, and this aspect warrants further investigation.

We also found that divergent thinking performance was associated with the cortical thickness of the left precuneus in the patients with BD. The importance of the precuneus in divergent thinking was also supported by one study demonstrating that individuals with higher verbal creative ability exhibited lower regional functional homogeneity in the right precuneus and that the cortical volume and thickness of the right precuneus were positively associated with individual verbal creativity (Q. L. Chen et al., 2015). The aforementioned results imply that individual differences in verbal creative thinking are reflected in the precuneus. The left precuneus is the core region of the default mode network, which is key to episodic memory retrieval and future simulation. Studies have highlighted the involvement of constructive episodic processes in creative cognition (Beaty, Thakral, Madore, Benedek, & Schacter, 2018) (Thakral, Madore, Kalinowski, & Schacter, 2020) and have suggested that the default mode network is causally linked to creative thinking (Shofty et al., 2022). In addition, one fMRI study identified stronger connectivity between the default mode network and a frontoparietal

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

brain network linked to cognitive control during divergent thinking (Madore, Thakral, Beaty, Addis, & Schacter, 2017). Taken with our findings regarding the right rostral middle frontal gyrus and left precuneus, the aforementioned findings indicate that divergent thinking involves the cooperation of different functional networks and the default mode network in patients with BD.

The present study identified a negative correlation between ATTA score and the cortical thicknesses of the frontal, parietal, and occipital structures. One interpretation of this result is that cortical thinness indicates cortical efficiency. A developmental study found that superior attentional performance is associated with a thinner cortex in bilateral frontoparietal networks and that individuals with higher maturity (i.e., individuals with thinner cortexes in these regions) activate the frontoparietal attentional network to a greater extent (Lu et al., 2009). Several studies have also reported a negative correlation between cortical thickness and divergent thinking performance in healthy individuals and have suggested that development of cognitive capacity (including creative capacity) can be associated with low cortical thickness in discrete regions of the brain (Jung et al., 2010; Tian et al., 2018). However, patients with psychiatric disorders have cortical thinness in various cortical structures and also exhibit considerable impairments in cognitive functions requiring executive control, such as working memory. Therefore, the relationship between cortical thinness and brain function might be complex, and the finding that cortical thinness is associated with superior divergent thinking performance in patients with BD should be interpreted cautiously.

In contrast with its cortical thickness, the surface area of the right superior frontal gyrus was positively correlated with ATTA score. One study found that a high-creative-achievement group exhibited significantly larger cortical surface areas of the right postcentral gyrus and bilateral superior parietal area than did HCs (Chrysikou et al., 2020). Another study found that professional comedians had larger cortical surface areas of the left inferior temporal gyrus, angular gyrus, precuneus, and right medial prefrontal cortex than did regular people (Brawer & Amir, 2021). Two studies demonstrated that patients with BD were associated with an increased cortical surface area of the pars triangularis (Yalin et al., 2019) (Woo et al., 2021). Therefore, increased surface area in the cortical structures of patients with BD might indicate a link between creativity and BD.

Several methodological limitations and alternative conceptualizations of our findings merit consideration. At first, the participants with BD were receiving various dosages of antipsychotics, antidepressants, antiepileptics, and lithium. A large-scale SBM study of patients with BD (1837 patients with BD, 2582 controls) found that increased cortical

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

thickness and surface area were associated with taking lithium, reduced cortical thickness was associated with antiepileptic treatment, and reduced cortical surface area was associated with atypical antipsychotic treatment. The aforementioned study did not detect any significant change in cortical thickness or surface area associated with antidepressant treatment. Therefore, the use of various psychotropics distinctly affects cortical thickness and surface area and should be considered a confounder in the present study. Secondly, the study found no statistically significant difference in the performance on the ATTA between patients with BD and HCs. Our behavioral findings did not support the hypothesis that patients with BD exhibit superior performance in creative thinking. Consequently, it is suggested that measures of divergent thinking may not be appropriate for identifying biomarkers or differentiating diagnostic criteria for the disease. Thirdly, a major concern regarding the findings pertains to elucidating the varied structural correlates of divergent thinking, particularly in light of the absence of significant differences in behavioral performance. We posited that these findings could be ascribed to the reorganization of brain function linked with prefrontal dysfunction in individuals with BD, although additional experimental evidence is necessary to substantiate our hypothesis. Finally, sex was not included as a nuisance covariate in our analysis based on evidence from prior studies suggesting that the majority of sex-related variations in neuroanatomical volume can be attributed to intracranial volume (Pintzka et al., 2015), and behavioral differences between sexes primarily relate to disparities in brain structure, largely influenced by variations in brain size (van Eijk et al., 2021; Eliot et al., 2023). Nonetheless, we conducted an additional analysis exploring the association between ATTA performance and cortical thickness/surface area with sex added as a covariate of no interest in patients with BD. While cortical surface area findings remained consistent, results for cortical thickness diverged significantly (detailed in supplementary Table 1). Therefore, it is important to acknowledge that sex may potentially impact our findings, and interpretations of the study should be approached cautiously in this regard.

Conclusion

Our findings indicate that divergent thinking involves multiple structures for executive control, mental imagery, and visual processing in patients with BD. The right prefrontal cortex exhibited the most significant correlation with behavioral performance in patients with BD, which might be attributable to its critical role in coordinating different cognitive process components during divergent thinking.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Acknowledgments

This study was supported by grants from Taiwan's National Science and Technology Council (NSC-103-2314-B-075-065-MY2, NSC 102-2420-H-010-003, and NSC 103-2420-H-010-001) and Taipei Veterans General Hospital (V104C-128).

Author contributions

YHK and TPS initiated the study. PCT and WCC performed statistical analyses and data interpretation, under the supervision of TPS. TPS, MHC and YHK collected data. All authors contributed to the data interpretation. PCT wrote the first draft of the manuscript and all authors edited and approved it for publication.

Competing interests

The authors declare no competing interests.

Ethics approval statement for work involving human subjects

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Significant Outcomes

- Divergent thinking involves cerebral structures for executive control, mental imagery, and visual processing in patients with BD.
- The right prefrontal cortex might be the most crucial of these structures.
- The present study identified a negative correlation between ATTA score and the cortical thicknesses of the frontal, parietal, and occipital structures that cortical thinness indicates cortical efficiency.

Limitations

- The participants with BD were receiving various dosages of antipsychotics, antidepressants, antiepileptics, and lithium. Therefore, the use of various psychotropics distinctly affects cortical thickness and surface area and should be considered a confounder in the present study.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

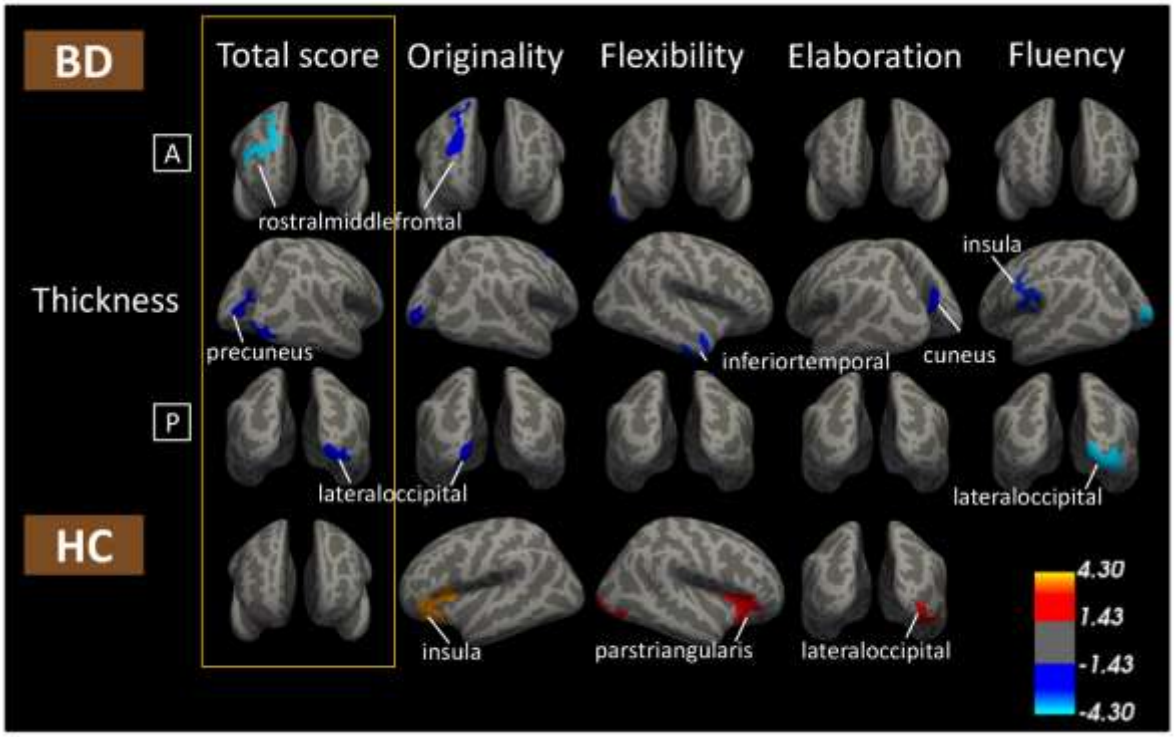

Figure 1. Cortical thickness correlates of divergent thinking measured by Abbreviated Torrance Test for Adults (ATTA) in patients with bipolar disorder and healthy controls. In patients with bipolar disorder, total ATTA score was negatively correlated with cortical thickness in the right middle frontal gyrus, right occipital, and left precuneus. In contrast, total ATTA scores and cortical thickness were not significantly correlated among the controls. BD=bipolar disorder; A=anterior; P=posterior.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

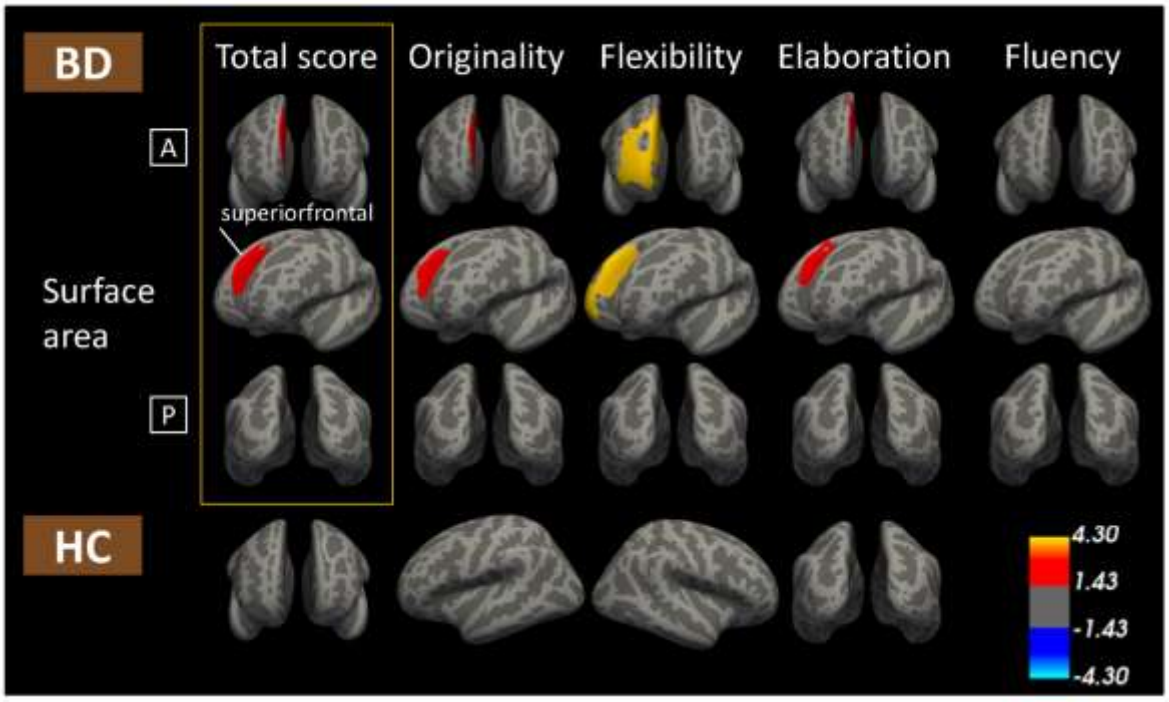

Figure 2. Cortical surface area correlates of divergent thinking in patients with bipolar disorder and healthy controls. In patients with bipolar disorder, total ATTA score was positively correlated with surface area of right superior frontal gyrus. In contrast, total ATTA scores and surface area were not significantly correlated among the controls.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Reference

Beaty RE, Thakral PP, Madore KP, et al. (2018) Core Network Contributions to Remembering the Past, Imagining the Future, and Thinking Creatively. *J Cogn Neurosci* 30: 1939-1951.

Brawer J and Amir O. (2021) Mapping the 'funny bone': neuroanatomical correlates of humor creativity in professional comedians. *Soc Cogn Affect Neurosci* 16: 915-925.

Cavanna AE and Trimble MR. (2006) The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129: 564-583.

Chen CY. (2006) *Abbreviated Torrance Test for Adults manual in Chinese Version*, Taipei: Psychology Publisher.

Chen QL, Xu T, Yang WJ, et al. (2015) Individual differences in verbal creative thinking are reflected in the precuneus. *Neuropsychologia* 75: 441-449.

Chrysikou EG, Wertz C, Yaden DB, et al. (2020) Differences in brain morphometry associated with creative performance in high- and average-creative achievers. *Neuroimage* 218: 116921.

Cogdell-Brooke LS, Sowden PT, Violante IR, et al. (2020) A meta-analysis of functional magnetic resonance imaging studies of divergent thinking using activation likelihood estimation. *Human Brain Mapping* 41: 5057-5077.

Dale AM, Fischl B and Sereno MI. (1999) Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction. *Neuroimage* 9: 179-194.

de Souza LC, Guimarães HC, Teixeira AL, et al. (2014) Frontal lobe neurology and the creative mind. *Front Psychol* 5: 761.

Eliot L, Beery AK, Jacobs EG, et al. (2023) Why and How to Account for Sex and Gender in Brain and Behavioral Research. *J Neurosci* 43: 6344-6356.

Fink A, Koschutnig K, Hutterer L, et al. (2014) Gray matter density in relation to different facets of verbal creativity. *Brain Struct Funct* 219: 1263-1269.

First MB, Spitzer RL, Gibbon M, et al. (1997) *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*: American Psychiatric Press.

Fischl B and Dale AM. (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences* 97: 11050-11055.

Fischl B, Sereno MI and Dale AM. (1999a) Cortical Surface-Based Analysis: II: Inflation, Flattening, and a Surface-Based Coordinate System. *Neuroimage* 9: 195-207.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Fischl B, Sereno MI, Tootell RBH, et al. (1999b) High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping* 8: 272-284.

Goff K and Torrance EP. (2002) *Abbreviated Torrance Test for Adults manual*, Bensenville, IL: Scholastic Testing Service, Inc.

Hamilton M. (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23: 56-62.

Jauk E, Neubauer AC, Dunst B, et al. (2015) Gray matter correlates of creative potential: a latent variable voxel-based morphometry study. *Neuroimage* 111: 312-320.

Jung RE, Segall JM, Jeremy Bockholt H, et al. (2010) Neuroanatomy of creativity. *Hum Brain Mapp* 31: 398-409.

Kubera KM, Schmitgen MM, Maier-Hein KH, et al. (2018) Differential contributions of cortical thickness and surface area to trait impulsivity in healthy young adults. *Behav Brain Res* 350: 65-71.

Kuperberg GR, Broome MR, McGuire PK, et al. (2003) Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 60: 878-888.

Kyaga S, Landen M, Boman M, et al. (2013) Mental illness, suicide and creativity: 40-year prospective total population study. *J Psychiatr Res* 47: 83-90.

Lu LH, Dapretto M, O'Hare ED, et al. (2009) Relationships between brain activation and brain structure in normally developing children. *Cereb Cortex* 19: 2595-2604.

Madore KP, Thakral PP, Beaty RE, et al. (2017) Neural Mechanisms of Episodic Retrieval Support Divergent Creative Thinking. *Cerebral Cortex* 29: 150-166.

Mayseless N, Eran A and Shamay-Tsoory SG. (2015) Generating original ideas: The neural underpinning of originality. *Neuroimage* 116: 232-239.

Minds S. (1969) Manual of SA creativity test. *Tokyo, Japan: Tokyo Shinri Corporation.[Google Scholar]*.

Pintzka CW, Hansen TI, Evensmoen HR, et al. (2015) Marked effects of intracranial volume correction methods on sex differences in neuroanatomical structures: a HUNT MRI study. *Frontiers in Neuroscience* 9.

Richards R, Kinney DK, Lunde I, et al. (1988) Creativity in manic-depressives, cyclothymes, their normal relatives, and control subjects. *J Abnorm Psychol* 97: 281-288.

Rosas HD, Liu AK, Hersch S, et al. (2002) Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 58: 695-701.

Santosa CM, Strong CM, Nowakowska C, et al. (2007) Enhanced creativity in bipolar disorder patients: a controlled study. *J Affect Disord* 100: 31-39.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Sheehan DV, Lecrubier Y, Sheehan KH, et al. (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20: 22-33;quiz 34-57.

Shofty B, Gonen T, Bergmann E, et al. (2022) The default network is causally linked to creative thinking. *Mol Psychiatry* 27: 1848-1854.

Sun J, Chen Q, Zhang Q, et al. (2016) Training your brain to be more creative: brain functional and structural changes induced by divergent thinking training. *Hum Brain Mapp* 37: 3375-3387.

Takeuchi H, Kimura R, Tomita H, et al. (2021) Polygenic risk score for bipolar disorder associates with divergent thinking and brain structures in the prefrontal cortex. *Hum Brain Mapp* 42: 6028-6037.

Takeuchi H, Taki Y, Sassa Y, et al. (2010) Regional gray matter volume of dopaminergic system associate with creativity: evidence from voxel-based morphometry. *Neuroimage* 51: 578-585.

Thakral PP, Madore KP, Kalinowski SE, et al. (2020) Modulation of hippocampal brain networks produces changes in episodic simulation and divergent thinking. *Proc Natl Acad Sci U S A* 117: 12729-12740.

Tian F, Chen Q, Zhu W, et al. (2018) The association between visual creativity and cortical thickness in healthy adults. *Neuroscience Letters* 683: 104-110.

Tu PC, Kuan YH, Li CT, et al. (2017) Structural correlates of creative thinking in patients with bipolar disorder and healthy controls-a voxel-based morphometry study. *J Affect Disord* 215: 218-224.

van Eijk L, Zhu D, Couvy-Duchesne B, et al. (2021) Are Sex Differences in Human Brain Structure Associated With Sex Differences in Behavior? *Psychological Science* 32: 1183-1197.

Woo Y, Kang W, Kang Y, et al. (2021) Cortical Thickness and Surface Area Abnormalities in Bipolar I and II Disorders. *Psychiatry Investig* 18: 850-863.

Wu X, Yang W, Tong D, et al. (2015) A meta-analysis of neuroimaging studies on divergent thinking using activation likelihood estimation. *Hum Brain Mapp* 36: 2703-2718.

Yalin N, Saricicek A, Hidiroglu C, et al. (2019) Cortical thickness and surface area as an endophenotype in bipolar disorder type I patients and their first-degree relatives. *Neuroimage Clin* 22: 101695.

Young RC, Biggs JT, Ziegler VE, et al. (1978) A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 133: 429-435.

Zhu F, Zhang Q and Qiu J. (2013) Relating inter-individual differences in verbal creative thinking to cerebral structures: an optimal voxel-based morphometry study. *PLoS One* 8.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Table 1. The demographic data and behavioral performance of participants in this study.

	BD N=59	HC N=56	t /X^2	p
Age	35.5±8.6	33.9±7.6	1.06	0.29
Sex (M/F)	28/31	22/34	0.78	0.45
Education	14.9±2.1	16.6±1.6	-4.29	<0.001
Age onset	23.2±7.2			
Duration of illness	11.1±6.5			
Age onset of manic	25.4±8.4			
Age onset of depression	22.9±6.9			
Manic / depression ratio	0.97±1.02			
Diagnosis (BD-I/BD-II)	27/32			
YMRS	3.2±2.9			
HDRS-17	3.6±3.0			
ATTA				
total score (creativity index)	67.37±7.33	67.93±5.90	-0.45	0.66
fluency	15.10±1.99	15.30±1.70	-0.58	0.56
originality	13.85±2.42	13.30±2.19	1.26	0.21
elaboration	16.73±1.51	16.63±1.59	0.36	0.72
flexibility	15.25±2.26	15.55±2.33	-0.70	0.49
verbal	1.37±1.19	1.27±1.09	0.49	0.62
figure	5.15±2.94	5.93±2.50	-1.52	0.13
Medication				
Antipsychotics (n)	23			
Antidepressants (n)	28			
Anti-epileptics (n)	32			
Lithium (n)	7			

BD=bipolar disorder; HC=healthy control; M=Male; F=Female; SD=standard deviation; YMRS=Young Mania Rating Scale; HDRS-17=17-item Hamilton Depression Rating Scale; ATTA= Abbreviated Torrance Test for Adults.

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press

Table 2. The cortical structures showing significant correlations between performance of divergent thinking and cortical thickness or surface areas in patients with bipolar disorder and controls.

	ATTA	Max	Cluster size (mm^2)	TalX	TalY	TalZ	Corrected P value	Structure
Cortical thickness								
BD								
	Total score	**-4.13**	**1582.0**	**22.8**	**45.8**	**19.7**	**0.000**	**R. rostralmiddlefrontal**
		-3.04	**877.5**	**20.5**	**-96.9**	**-5.5**	**0.020**	**R. lateraloccipital**
		-2.87	**846.7**	**-19.7**	**-68.3**	**20.1**	**0.024**	**L. precuneus**
	Originality	-4.30	1145.1	22.9	46.1	21.2	0.003	R. rostralmiddlefrontal
		-3.04	807.7	-12.3	-94.3	-4.0	0.032	L. lateraloccipital
	Flexibility	-3.81	1235.9	50.0	-11.4	-31.0	0.001	R. inferiortemporal
	Elaboration	-2.88	779.9	5.0	-66.2	19.1	0.038	R. cuneus
	Fluency	-4.31	1698.6	30.0	-87.8	3.4	0.000	R. lateraloccipital
		-3.45	1343.7	-34.0	-28.1	21.1	0.001	L. insula
HC								
	Originality	5.02	1206.1	36.6	30.5	-2.0	0.004	R. parstriangularis
		3.64	1622.5	-25.2	11.9	-14.3	0.000	L. insula
		2.35	905.0	29.5	-89.4	3.5	0.030	R. lateraloccipital
Surface area								
BD								
	Total score	**5.67**	**1564.5**	**13.8**	**41.1**	**14.9**	**0.007**	**R. superiorfrontal**
	Originality	3.33	1253.9	12.2	42.7	15.9	0.033	R. superiorfrontal
	Flexibility	5.89	4838.0	13.1	42.5	14.2	0.000	R. superiorfrontal
	Elaboration	3.91	1365.6	9.8	34.4	26.4	0.019	R. superiorfrontal
HC								

Max = Maximum voxel-wise significance in cluster; Size = Surface area of cluster; TalX, TalY, TalZ = Talairach coordinate of maximum;

https://doi.org/10.1017/neu.2024.17 Published online by Cambridge University Press