

# Association between cortical thickness or surface area and divergent thinking in patients with bipolar disorder

## Original Article

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### 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 ( $35.3 \pm 8.5$  years) and 56 age- and sex-matched controls ( $33.9 \pm 7.4$  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.

### Significant outcomes

- Divergent thinking involves cerebral structures for executive control, mental imagery, and visual processing in patients with bipolar disorder (BD).
- The right prefrontal cortex might be the most crucial of these structures.
- The present study identified a negative correlation between Abbreviated Torrance Test for Adults 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.

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### Introduction

Bipolar disorder (BD) is a major psychiatric disorder characterised 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 *et al.*, 1998). 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 grey 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 *et al.*, 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 processes, 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 utilising voxel-based morphometry (VBM) have delineated a correlation between performance in divergent thinking tasks and grey 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 grey 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-use tasks and three-instance tasks, unveiling an association between ideational originality and grey matter volume in the precuneus and caudate nucleus (Jauk *et al.*, 2015). Additionally, a study utilising the S-A creativity test (Minds, 1969) detected positive correlations between individual creativity and regional grey matter volume in the right dorsolateral prefrontal cortex, bilateral striatum, substantia nigra, tegmental ventral area, and periaqueductal grey (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 grey 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 grey matter volume of the dorsal part of the right medial prefrontal cortex (Brodmann area 9) in patients with BD, and the study emphasised the importance of cognitive control in creative thinking (Tu *et al.*, 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 grey matter and might contribute differently to individual differences in behaviour, 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 on divergent thinking tasks and the cortical thickness or surface area of the prefrontal cortex among individuals diagnosed with 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 *et al.*, 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). A total of 56 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 enrolment process in Supplementary Figure 1). All procedures were approved

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

	BD	HC	<i>t</i> / $\chi^2$	<i>p</i>
	<i>N</i> = 59	<i>N</i> = 56		
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			
Antiepileptics (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.

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.

### Measurement of divergent thinking

We adopted the Chinese version of the Abbreviated Torrance Test for Adults (ATTA) (Goff & Torrance, 2002), which was edited by 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 MRI system (3.0T GE Discovery MR750). Head stabilisation 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 = 8.38 ms, echo time = 3.54 ms, inversion time = 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 analysed using FreeSurfer (version 7.0, [www.nmr.mgh.harvard.edu/martinos](http://www.nmr.mgh.harvard.edu/martinos)) to create anatomical surface models and for statistical analyses (Dale *et al.*, 1999; Fischl *et al.*, 1999a, 1999b). For each participant, the processing stream included the removal of nonbrain tissue, transformation to Talairach space, and segmentation of grey–white matter tissue. The thickness measurements across the cortex were computed by determining the point on the grey–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 grey–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 *et al.*, 1999a, 1999b). For vertex-by-vertex cluster analysis, the thickness or surface area maps of all participants in both groups were converted to a common atlas space (Fischl *et al.*, 1999a, 1999b). 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 artefacts 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 1 patient with BD were excluded due to quality control.

### Statistical analyses

We employed the query, design, estimate, and 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 analyse 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  $p < 0.01$  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  $p < 0.05$  were reported. The correlation between divergent thinking and cortical thickness or surface area was analysed 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 behavioural 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 (Fig. 1, Table 2). By contrast, ATTA score correlated positively with the surface area of the right superior frontal gyrus (Fig. 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 (Fig. 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 (Fig. 2, Table 2). In the HCs, originality and the cortical thicknesses of the right inferior frontal, occipital, and left insula were positively correlated (Fig. 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 utilising 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 cortical structure and behavioural 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.

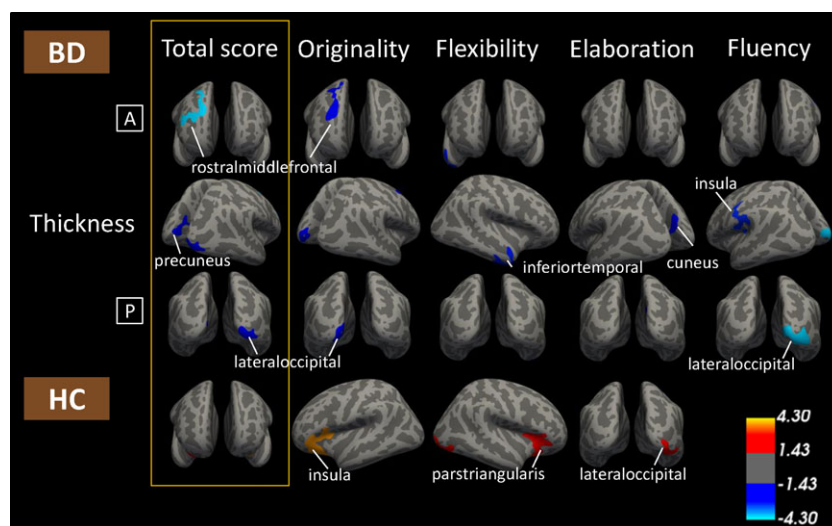
The most significant correlation and largest cluster were obtained for the right rostral middle frontal gyrus. The right middle frontal gyrus is a key node of the executive control network, and our findings indicate that executive control might have a critical influence on divergent thinking performance 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 *et al.*, 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



**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 <sup>2</sup> )	TalX	TalY	TalZ	Corrected P value	Structure
<i>Cortical thickness</i>							
BD							
<b>Total score</b>	<b>-4.13</b>	<b>1582.0</b>	<b>22.8</b>	<b>45.8</b>	<b>19.7</b>	<b>0.000</b>	<b>R. rostral middle frontal</b>
	<b>-3.04</b>	<b>877.5</b>	<b>20.5</b>	<b>-96.9</b>	<b>-5.5</b>	<b>0.020</b>	<b>R. lateral occipital</b>
	<b>-2.87</b>	<b>846.7</b>	<b>-19.7</b>	<b>-68.3</b>	<b>20.1</b>	<b>0.024</b>	<b>L. precuneus</b>
Originality	-4.30	1145.1	22.9	46.1	21.2	0.003	R. rostral middle frontal
	-3.04	807.7	-12.3	-94.3	-4.0	0.032	L. lateral occipital
Flexibility	-3.81	1235.9	50.0	-11.4	-31.0	0.001	R. inferior temporal
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. lateral occipital
	-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. pars triangularis
	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. lateral occipital
<i>Surface area</i>							
BD							
<b>Total score</b>	<b>5.67</b>	<b>1564.5</b>	<b>13.8</b>	<b>41.1</b>	<b>14.9</b>	<b>0.007</b>	<b>R. superior frontal</b>
Originality	3.33	1253.9	12.2	42.7	15.9	0.033	R. superior frontal
Flexibility	5.89	4838.0	13.1	42.5	14.2	0.000	R. superior frontal
Elaboration	3.91	1365.6	9.8	34.4	26.4	0.019	R. superior frontal
HC							

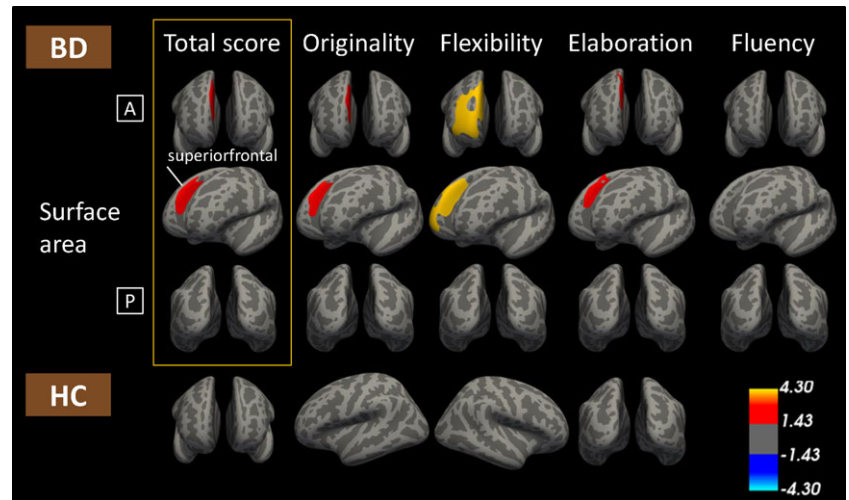
ATTA = Abbreviated Torrance Test for Adults; Max = maximum voxel-wise significance in cluster; TalX, TalY, TalZ = Talairach coordinate of maximum; BD = bipolar disorder; HC = healthy control.



**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.

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).



**Figure 2.** Cortical surface area correlates of divergent thinking in patients with bipolar disorder and healthy controls. In patients with bipolar disorder, total Abbreviated Torrance Test for Adults (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.

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 (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 *et al.*, 2018; Thakral *et al.*, 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 brain network linked to cognitive control during divergent thinking (Madore *et al.*, 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 the 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 conceptualisations 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 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 behavioural 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 behavioural performance. We posited that these findings could be ascribed to the reorganisation 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 behavioural 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 behavioural performance in patients with BD, which might be attributable to its critical role in coordinating different cognitive process components during divergent thinking.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/neu.2024.17>.

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**Author contribution.** 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.

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