Brain Entropy is Associated with Divergent Thinking

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Abstract

Creativity is the ability to generate original and useful products, and it is considered central to the progression of human civilization. As a non-inherited emerging process, creativity may stem from temporally dynamic brain activity, which, however, has not been well studied. The purpose of this study was to measure brain dynamics using entropy and to examine the associations between brain entropy (BEN) and divergent thinking in a large healthy sample. The results showed that divergent thinking was consistently positively correlated with regional BEN in the left dorsal anterior cingulate cortex/pre-supplementary motor area and left dorsolateral prefrontal cortex, suggesting that creativity is closely related to the functional dynamics of the control networks involved in cognitive flexibility and inhibitory control. Importantly, our main results were cross-validated in two independent cohorts from two different cultures. Additionally, three dimensions of divergent thinking (fluency, flexibility and originality) were positively correlated with regional BEN in the left inferior frontal gyrus and left middle temporal gyrus, suggesting that more highly creative individuals possess more flexible semantic associative networks. Taken together, our findings provide the first evidence of the associations of regional BEN with individual variations in divergent thinking and show that BEN is sensitive to detecting variations in important cognitive abilities in healthy subjects.

Keywords: divergent thinking, brain entropy mapping (BEN), dorsolateral prefrontal cortex (DLPFC), semantic associative network

Introduction

Creativity is the ability to abstract or generate new knowledge or products and is central to the progression of human civilization, prosperity, and well-being (Runco MA and GJ Jaeger 2012; Diedrich J et al. 2015). Divergent thinking is a key component of creativity that has been found to predict future academic success and social adaptation (Baas M et al. 2008). Over the past decade, many studies have adopted functional neuroimaging to search for brain mechanisms that potentially explain creativity. Most have focused on brain activation during the performance of some “creative” task, such as a divergent thinking task (DTT, e.g., alternative uses task [AUT]) (Fink A et al. 2006; Fink A et al. 2009; Fink A et al. 2010; Abraham A et al. 2012; Kleibeuker SW et al. 2013; Cousijn J et al. 2014; Sun J et al. 2016). However, creativity is a vast and complex construct that requires the involvement of multiple brain regions or networks (Runco MA and S Acar 2012; Jung RE et al. 2013; Beaty RE et al. 2016). Previous task-fMRI studies that have mainly focused on task-dependent activation may reveal only the local activation of one or several brain regions during a specific creative task. Resting-state brain activity represents a baseline level of activation that is not specific to any overt task and accounts for most of the energy consumed by brain (Raichle ME et al. 2001). Therefore, a recent research interest is to examine the association between resting-state brain activity and creativity (Beaty RE, M Benedek, et al. 2014; Wei D et al. 2014; Chen Q-L et al. 2015; Zhu W et al. 2017; Beaty RE et al. 2018).

To date, the existing resting-state literature converges on the hypothesis that creativity is associated with the spontaneous activity of brain regions within and/or between the default mode network (DMN) and cognitive control network (CCN) (Takeuchi H et al. 2012; Beaty RE, M

Benedek*, et al.* 2014; Chen Q et al. 2014; Wei D *et al.* 2014; Li W et al. 2016; Zhu W *et al.* 2017). Most of these studies examined resting-state functional connectivity (FC), including seed-based FC (Takeuchi H *et al.* 2012; Beaty RE, M Benedek*, et al.* 2014; Wei D *et al.* 2014), large-scale brain network FC (Zhu W *et al.* 2017; Shi L et al. 2018) and voxel-wise functional connectivity strength (FCS) (Gao Z et al. 2017; Jiao B et al. 2017). Using the medial prefrontal cortex (mPFC), the core node of the DMN, as a seed region, Takeuchi et al. (2012) found that creativity measured by DTTs is positively correlated with the strength of mPFC and posterior cingulate cortex (PCC) connectivity. Similarly, Wei et al. (2014) found that verbal creativity is positively correlated with FC between the mPFC and middle temporal gyrus (MTG). These regions all belong to the DMN, suggesting that FC within the DMN is closely related to creativity. Using the key regions of the CCN, such as the dorsolateral prefrontal cortex (DLPFC) or inferior frontal gyrus (IFG), as the seed regions, previous studies have revealed that figural creativity is positively correlated with FC between the bilateral DLPFC (Li W *et al.* 2016) and that high-creative individuals exhibit increased FC between the IFG and the entire DMN in comparison with low-creative individuals (Beaty RE, M Benedek*, et al.* 2014). Based on these findings, creativity is closely related to executive-executive (within-network) coupling and default-executive (between-network) coupling. A large-scale brain network FC analysis further supports this hypothesis. Using an independent component analysis, Zhu et al. (2017) decomposed the brain into large-scale networks and then investigated the relationship between creativity and large-scale brain network FC; and found that both creative domains (visual and verbal creativity) are positively correlated with FC between the DMN and CCN. However, visual creativity was negatively correlated with within-network coupling (both within the posterior DMN and within the right CNN), and verbal creativity was negatively correlated with FC within the anterior DMN. In addition, based on FCS and graph theory analysis, previous studies found that more highly creative groups exhibit higher network efficiency (Jiao B *et al.* 2017) and better information transformation efficiency (Gao Z *et al.* 2017) than groups with lower levels of creativity. Furthermore, a study examining the relationship between verbal creativity and the dynamic reconfiguration of brain network FC reported that the temporal variability of FC patterns within the DMN, between the DMN and attention/sensorimotor network, and between the control and sensory networks correlate with verbal creativity, indicating that verbal creativity is associated with high variability of networks involved in spontaneous thought, cognitive control and attention (Sun J et al. 2018).

Two other resting-state brain activity metrics, regional homogeneity (ReHo) and fractional amplitude of low frequency fluctuations (fALFF), have also been used in imaging-creativity association studies. Chen et al. (2015) found that people with a high verbal creative ability exhibit low ReHo in the right precuneus. Additionally, based on a large sample (1277 subjects), Takeuchi et al. identified associations between verbal creativity and ReHo in the left anterior temporal lobe and fALFF in the precuneus, middle cingulate gyrus, right middle frontal gyrus and cerebellum (Takeuchi H et al. 2017). ReHo measures the temporal homogeneity of neural activity and reflects the inter-voxel coherence within the neighbouring voxels during rest (Zang Y et al. 2004), while fALFF measures the amplitude of neural activity and is thought to be a direct index of the spontaneous signal fluctuations during rest (Zang YF et al. 2007). However, these measures do not actually assess brain activity dynamics at the local voxel level. fALFF is the only measure that can partially examines the temporal dynamics but it has a purely empirical cut-off threshold. Assessment of full-band temporal dynamics may reveal important brain-behaviour relationships.

In contrast to other resting-state brain measures such as ALFF and ReHo, brain entropy (BEN) is a new method that has recently been developed to quantify the state of the temporal brain dynamics by measuring the signal regularity of a time series (Yang AC et al. 2013; Smith RX et al. 2014; Wang Z et al. 2014). Entropy is a well-defined physical and statistical concept that measures the complexity, randomness, and predictability of a dynamic process (Pincus SM 1991; Sandler SI 2017). The entropy value reflects the extent to which a signal is temporally ordered (low entropy), complex (medium entropy), or uncorrelated (high entropy). Recently, BEN was defined as the number of neural states a given brain can access (Saxe GN et al. 2018). The human brain is a dynamic functional system that exhibits ongoing fluctuations in activity and its dynamic range relates to the information processing capacity (Xue S-W et al. 2019). A brain capable of large variability in neural states will more easily understand and predict variable external events. Therefore, a higher BEN value indicates a large information processing capacity and irregularities in brain activity. A previous study that examined the relationship between brain entropy and intelligence identified a positive correlation between BEN at rest and individuals' intellectual ability, suggesting that access to variable neural states predicts complex behavioural performance (Saxe GN et al. 2018). Thus, BEN is an emerging method that characterizes the resting-state temporal dynamics of the brain and represents a physiologically meaningful approach to assess the dynamic status of intrinsic activity in temporal patterns (Bassett DS et al. 2012; Wang Z et al. 2014).

BEN mapping is still new in the literature, although it has successfully been applied in several neuroimaging studies. Regional BEN has been reliably mapped in the normal brain (Wang Z *et al.* 2014). However, the normal BEN distribution may be altered during ageing (Yao Y et al. 2013), and in patients with attention deficit hyperactivity disorder (Sokunbi MO et al. 2013), schizophrenia (Sokunbi MO et al. 2014), smoking habits (Li Z et al. 2016), and cocaine addiction (Wang Z et al. 2017). For example, patients with Alzheimer's disease exhibit lower entropy values in the frontal, temporal, and occipital lobes than healthy controls (Wang B et al. 2017) while patients with relapsing-remitting multiple sclerosis patients show increased BEN in the motor areas, spatial coordination areas, memory areas and executive control areas compared with controls (Zhou F et al. 2016). Additionally, a study applying BEN to a healthy sample found that compared with controls, chronic smokers exhibited globally higher BEN (Li Z et al. 2016). However, most of these studies focused on the comparison between two groups (e.g., patients vs. healthy controls), and few studies have directly examined the relationship between regional BEN and individual differences in behavioural variables, such as divergent thinking.

The purpose of the present study was to investigate the relationship between regional BEN and divergent thinking using resting-state fMRI from a large cohort of healthy subjects. Given that previous studies have shown that creativity is associated with the dynamic interactions among the DMN, SN and CCN (Beaty RE et al. 2016; Zhu W *et al.* 2017; Beaty RE *et al.* 2018; Sun J *et al.* 2018), we hypothesized that divergent thinking is associated with the entropy value of brain regions within the DMN (e.g., the PCC and MTG), SN (e.g., the dorsal ACC [dACC]) and CCN (e.g., the DLPFC and IFG). First, individuals' divergent thinking scores were assessed using the verbal form of Torrance Tests of Creative Thinking (TTCT) (Torrance E 1974). Then, the whole-brain BEN map was computed using the Brain Entropy Mapping toolbox (BENtbx) (Wang Z et al. 2014). Finally, a correlation analysis was performed to examine the relationship between regional BEN and individual differences in divergent thinking. In addition, we attempted to replicate the results in two independent samples to improve the reliability and strength of our work.

Materials and Methods

Participants

The main sample was drawn from the time point 1 (T1) data of the Southwest University Longitudinal Imaging Multimodal (SLIM) Dataset (INDI, http://fcon_1000.projects.nitrc.org/) (Liu W et al. 2017). This sample consists of 401 college students recruited from Southwest University. All participants were healthy and right-handed, with no history of neurological or psychological disorders and provided written informed consent. All participants were required to complete behaviour tests (including a creativity test and intelligence tests) and brain imaging data acquisition. Fifteen subjects were excluded due to the absence of imaging data, leaving a final sample of 386 subjects (182 males), aged 17-27 years (mean ± standard deviation [SD] = 20.0 ± 1.16). The study was approved by the Southwest University Brain Imaging Center Institutional Review Board.

Assessment of Divergent Thinking

The verbal form of the Chinese version TTCT (Torrance E 1974; Ye R et al. 1988) has often been used to assess an individual's divergent thinking ability, which is a core aspect of creativity (Runco MA and S Acar 2012). It consists of seven subtasks (Torrance E 1974). Three subtasks require subjects to respond to a scenario presented pictorially by generating questions, causes and consequences for 5 minutes. The fourth subtask requires subjects to improve a product (toy elephant) by proposing creative ideas for 10 minutes. The fifth subtask requires subjects to generate as many unusual uses of a cardboard box as possible within 10 minutes. The sixth subtask requires subjects to generate unusual questions related to a cardboard box for 5 minutes. The seventh subtask requires subjects to imagine the consequences of an impossible situation for 5 minutes. For each subtask, the scores comprise 3 different creative dimensions: fluency (the number of relevant and meaningful responses), flexibility (the number of different categories of responses), and originality (the degree of originality of the responses). Three trained raters evaluated the responses recorded in all tasks, and the inter-rater correlation coefficient was high (0.9). The total score was the sum of the fluency, flexibility, and originality scores of all subtasks.

Assessment of General Intelligence

The Combined Raven's Test (CRT; Chinese revised edition) was used to examine subjects' intellectual ability (Wang D et al. 2006). This test displays good reliability and validity (Ming WDQ 1989; Tang C et al. 2012). The CRT contains three Raven's standard progressive matrices (C, D, and E sets) and three Raven's colour progressive matrices (A, B, and AB sets), with a total of 72 nonverbal items. Participants were asked to choose the correct answer from six or eight alternatives by completing the matrix with a missing piece. The intelligence score is equal to the number of correct answers.

Image Acquisition

All structural and functional MRI scans were performed on a 3T Trio scanner (Siemens Medical Systems, Erlangen, Germany) at the Brain Imaging Center, Southwest University. Resting-state fMRI (rs-fMRI) images were obtained using a gradient echo-planar imaging sequence: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, slices = 32, thickness = 3 mm, resolution matrix = 64 × 64, flip angle = 90º, field of view (FOV) = 220 × 220 mm^2, and voxel size = 3.4 × 3.4 × 4 mm^3. High-resolution T1-weighted structural images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence: TR/TE = 1900 ms/2.52 ms, inversion time = 900 ms, flip angle = 9°, FOV= 256 × 256 mm^2, slices = 176, thickness = 1.0 mm, and voxel size = 1 × 1 × 1 mm^3.

Image Preprocessing and BEN Mapping

Data preprocessing was performed using batch scripts provided with ASLtbx (Wang Z et al. 2008) based on SPM (http://www.fil.ion.ucl.ac.uk/spm/). Briefly, the first 10 volumes of rs-fMRI images were discarded to allow the signal to reach a steady state. The remaining rs-fMRI images were corrected for slice timing and head motion. The high-resolution structural images were first reoriented to the original image and then segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the segmentation tool in SPM8. Then, rs-fMRI images were registered to the Montreal Neurological Institute (MNI) standard space via the T1-weighted anatomical images. Subsequently, temporal nuisance filtering was performed (including bandpass filtering [0.01-0.08 Hz] and nuisance correction [head motion parameters, WM and CSF signals]) and then smoothed with a 6 mm full-width half-maximum (FWHM) Gaussian kernel.

After preprocessing, each subjects's BEN map was computed using the BENtbx (https://cfn.upenn.edu/~zewang/BENtbx.php) (Wang Z et al. 2014). BEN was calculated at each voxel using Sample Entropy (SampEn) (Lake DE et al. 2002). SampEn is one of the approximate entropy measures that quantifies the temporal coherence of a time series by computing the 'logarithmic likelihood' that a small section (within a window of length 'm') of the data that matches with other sections will still match the others if the section length increases by 1. 'Match' is defined by a cut-off threshold 'r'. Based on previous studies (Wang Z et al. 2014), the optimal window length 'm' was set to 3 and the optimal cut-off threshold 'r' was set to 0.6. The entropy values for all voxels that formed the BEN map, were calculated using the 'batch_calc_BEN' code in BENtbx. Subsequently, the BEN map was normalized to the MNI standard space using SPM8 and resampled with a resolution of 2 x 2 x 2 mm^3 and then smoothed with an isotropic Gaussian kernel (FWHM = 6 mm^3).

BEN-Behaviour Correlation Analysis

A multiple regression analysis was performed using SPM8 to explore the brain regions in which the regional BEN value was correlated with the creativity score. Age, sex and the intelligence score were included as nuisance covariates. The small-volume correction (SVC) method was performed across the regions of interest (ROIs) defined by previous studies (Fink A et al. 2009; Abraham A et al. 2012; Jung EK et al. 2013; Chen Q et al. 2014; Wu X et al. 2015; Beaty RE et al.

2016). The statistical significance level was set at $p < 0.05$, with SVC for multiple comparisons (family-wise error, FWE corrected) in ROIs. These ROIs are all key nodes of the DMN, CCN and SN, including the PCC, MTG, DLPFC, IFG, and dACC, and were created using the Wake Forest University (WFU) Pick Atlas (Maldjian JA et al. 2003).

Validation Analysis

To improve the strength and reliability of our work, we validated our main results in two independent samples (see **SI Materials and Methods**). First, we produced binary masks for those regions that showed a significant correlation with divergent thinking in the main findings. Then, each region's average entropy value was extracted from the BEN map in two independent samples by applying the above binary masks described above. Finally, a partial correlation analysis was performed to examine whether the entropy values of these regions also correlated with individuals' divergent thinking in the two independent samples after regressing out the age, sex, and intelligence score. Multiple comparisons were performed using the false discovery rate (FDR).

Results

Behavioural Assessments

Table 1 shows the means and standard deviations of the demographic and behavioural assessments of all subjects involved in the present study.

BEN-Behaviour Correlation Analysis

First, no significant result was obtained after applying the voxel-level FWE correction ($p < 0.05$, cluster size > 10) at the whole-brain level. Then, based on our strong hypothesis, the SVC method ($p < 0.05$, FWE-corrected) was used for multiple comparisons. The results are presented in Figure 1 and Table 2. Significant positive correlations between the total creativity score and regional BEN were observed in the left dACC extending into the pre-supplementary motor area (dACC/pre-SMA, cluster size = 44 voxels; peak coordinates in MNI: x, y, z = -8, 18, 54, t_{peak} = 4.99, r = 0.222, $p_{(svc)} < 0.05$), left DLPFC (cluster size = 154 voxels; peak coordinates in MNI: x, y, z = -16, 40, 50, t_{peak} = 3.82, r = 0.220, $p_{(svc)} < 0.05$), left opercular region of the IFG (IFG_Oper: cluster size = 53 voxels; peak coordinates in MNI: x, y, z = -36, 16, 34, t_{peak} = 4.48, r = 0.223, $p_{(svc)} < 0.05$), and left triangular region of the IFG (IFG_Tri, cluster size = 66 voxels; peak coordinates in MNI: x, y, z = -56, 28, 26, t_{peak} = 4.13, r = 0.219, $p_{(svc)} < 0.05$). No significant negative correlation between the total creativity score and regional BEN in the brain was found.

Significant positive correlations between the three dimensions of divergent thinking and regional BEN were also observed in the resting brain (Figure 2 and Table 2). Positive correlations between flexibility and regional BEN were found in the left dACC/pre-SMA (cluster size = 42 voxels; peak coordinates in MNI space: x, y, z = -8, 18, 54, t_{peak} = 5.12, r = 0.214, $p_{(svc)} < 0.05$), left DLPFC (cluster size = 197 voxels; peak coordinates in MNI space: x, y, z = -16, 40,50, t_{peak} = 3.97, r = 0.184, $p_{(svc)} < 0.05$), left IFG_Oper (cluster size = 53 voxels; peak coordinates in MNI space: x, y, z = -36, 16, 34, t_{peak} = 4.62, r = 0.223, $p_{(svc)} < 0.05$), and left IFG_Tri (left: cluster size = 76 voxels; peak coordinates in MNI space: x, y, z = -56, 28, 26, t_{peak} = 4.51, r = 0.170, $p_{(svc)} < 0.05$). Positive correlations between fluency and regional BEN were observed in the left dACC/pre-SMA (cluster size = 51 voxels; peak coordinates in MNI space: x, y, z = -8, 18, 54, t_{peak} = 4.61, r = 0.220, $p_{(svc)} < 0.05$), left DLPFC (cluster size = 118 voxels; peak coordinates in MNI space: x, y, z = -16, 48, 34, t_{peak} = 3.72, r = 0.217, $p_{(svc)} < 0.05$), and left MTG (cluster size = 38 voxels; peak coordinates in MNI space: x, y, z = -56, -16, -12, t_{peak} = 4.31, r = 0.160, $p_{(svc)} < 0.05$). Positive correlations between originality and regional BEN were observed in the left dACC/pre-SMA (cluster size = 28 voxels; peak coordinates in MNI space: x, y, z = -8, 18, 54, t_{peak} = 4.38, r = 0.202, $p_{(svc)} < 0.05$) and left IFG_Oper (cluster size = 27 voxels; peak coordinates in MNI space: x, y, z = -38, 18, 34, t_{peak} = 3.97, r = 0.200, $p_{(svc)} < 0.05$).

Validation Analysis

The associations between BEN and divergent thinking identified in the main cohort were cross-validated in two independent cohorts.

Independent sample 1: This sample consisted of 431 Chinese subjects from the Gene-Brain-Behavior project of Southwest University. The behavioural and functional imaging tests were the same as those used in our main discovery dataset (see **SI Materials and Methods**). The validation results showed a positive correlation between the entropy value of the left dACC/pre-SMA and the total score (r = 0.134, p = 0.005), and the entropy value of the left DLPFC was marginally positively correlated with the total score (r = 0.094, p = 0.051) (Figure 3). Similarly, positive correlations between the entropy value of the left dACC/pre-SMA with originality (r = 0.146, p = 0.002) and flexibility (r = 0.141, p = 0.003), and between the entropy value of the left DLPFC with originality ($r = 0.103$, $p = 0.032$) and flexibility ($r = 0.108$ $p = 0.025$) were also observed (Figure 3).

Independent sample 2: This sample included 132 subjects from the University of North Carolina at Greensboro (UNCG) (Beaty RE et al. 2018). The subjects completed a different verbal creativity test, namely, the AUT (see **SI Materials and Methods**). However, consistent results were obtained. The regional entropy value of the left dACC/pre-SMA was positively correlated with the creativity score ($r = 0.232$, $p = 0.007$). Similarly, the entropy value of the left DLPFC was also positively correlated with the creativity score ($r = 0.195$, $p = 0.025$) (Figure 4).

Given that the discovery sample and independent sample 1 were both Chinese populations, we also combined the two Chinese samples to examine the relationship between creativity and resting brain entropy within a larger sample. A multiple regression analysis was performed on the combined sample, controlling for age, gender, mean FD, scanning session of two samples. The SVC method ($p < 0.05$ corrected) was also applied here for multiple comparisons. Similar results were observed whatever using the combined Chinese sample (see Table S2) or two separate Chinese samples.

Discussion

The present study aimed to examine the associations between regional BEN and divergent thinking using a large cohort of healthy subjects. BEN is an emerging brain activity measure that has been increasingly used to assess brain states but has rarely been used to assess normal cognitive abilities. Based on our results, divergent thinking is consistently positively correlated with the regional BEN of the left dACC/pre-SMA and left DLPFC in both the discovery dataset and two validation datasets. In addition, significant correlations were observed between the three dimensions of divergent thinking (flexibility, fluency and originality) and regional BEN in the left IFG and left MTG. Together, these findings provide the first evidence of the associations of regional BEN with individual variations in divergent thinking.

In this study, divergent thinking was found to be consistently positively correlated with the regional BEN of the left dACC/pre-SMA and left DLPFC in both the discovery dataset and two validation datasets, suggesting that highly creative individuals may exhibit more irregular and variable activity in these brain regions. This finding is consistent with results from a recent study reporting a correlation between verbal creativity and the temporal variability of the FC patterns of the control networks (Sun J et al. 2018). Creativity is closely related to the ability to switch between remote semantic concepts and organize them into creative associations in a flexible manner (Bossomaier T et al. 2009; Fink A et al. 2009), which may be reflected by brain variability or flexibility during the resting state. Larger variability of the left dACC/pre-SMA and left DLPFC in our results indicated more variable and flexible resting brain activity, which may facilitate executive functions that are subserved by these regions. Supporting evidence from previous studies revealed that the dACC/pre-SMA and DLPFC are implicated in various processes related to creativity. For example, the dACC/pre-SMA is often activated during different creative tasks, such as insight problem solving (Kounios J et al. 2008; Qiu J et al. 2010), word association (Bechtereva NP et al. 2004), divergent thinking (Carlsson I et al. 2000), and musical improvisation

(Bengtsson SL et al. 2007). The function of the dACC/pre-SMA is involved in the response selection and inhibition linked to response flexibility (Nee DE et al. 2007; Dosenbach NUF et al. 2008), supporting the executive control aspect of creative cognition (Manzano Öd and F Ullén 2012). Similarly, the main functions of the DLPFC are inhibitory control and cognitive flexibility (Miller EK and JD Cohen 2001; Koechlin E et al. 2003; Alvarez JA and E Emory 2006). The inhibitory control process points to the role of executive processes in suppressing ordinary responses (Benedek M et al. 2014), while cognitive flexibility is involved in the executive processes required for shifting fixed mindsets and applying novel criteria to combine remote concepts (Howard-Jones PA et al. 2005; Sawyer K 2011), all of which are crucial for creative information processing (Dietrich A 2004; Dietrich A and R Kanso 2010). For example, behavioural studies have reported a close association between higher creativity and higher cognitive flexibility (Zabelina DL and MD Robinson 2010; Benedek M, E Jauk, et al. 2014; Chen Q et al. 2014). As noted above, entropy is a measure of the variety of change patterns in a time-series signal and depicts irregularities in brain activity (Shannon CE and W Weaver 1950). A higher entropy value indicates large, irregular and variable brain fluctuations. Entropy is also related to the ability to shift among different states, which is defined as flexibility (Shuiabi E and V Thomsonab 2005). Supporting evidence from a resting-state fMRI study showed that BEN measured at rest reveals the overall flexibility or readiness of the brain to respond to unpredictable stimuli. This study even identified a close association between entropy in a variety of widespread brain regions and the performance on the Matrix Reasoning task, which requires flexible reasoning about novel stimuli (Saxe GN et al. 2018). Therefore, together with the previous finding that people who can easily shift between different concepts or states during creative problem solving and are capable of cognitive flexibility may obtain a high creativity score (Fink A et al. 2009), the large irregularity and variable brain fluctuations that are manifested as high entropy values may be closely related to cognitive flexibility during creative problem solving. Taken together, the high entropy of the left DLPFC in highly creative individuals suggests that creativity is closely related to the functional dynamics of the control networks involved in cognitive flexibility and inhibitory control.

In addition, a higher entropy value indicates higher frequency fluctuations. Technically, the presence of more high frequency fluctuations in correlated signals may reduce their correlation (Wang Z *et al.* 2014; Zhou F *et al.* 2016). Thus, a higher entropy value of the control network may reflect a weaker FC within the control network. Creativity is negatively associated with executive-executive (within-network) coupling during both resting-state and task-based fMRI (Zhu W *et al.* 2017; Shi L *et al.* 2018), which may partially support our findings of the positive correlations between verbal creativity and the regional entropy value of the control network.

In the present study, the three dimensions of divergent thinking (flexibility, fluency and originality) positively correlated with regional BEN in the left IFG and left MTG. Based on accumulating evidence, creativity is related to the involvement of the IFG and MTG. For example, structural MRI studies revealed associations between increased cortical thickness and/or volume of the bilateral IFG with higher verbal creativity (Takeuchi H et al. 2012; Zhu F et al. 2013). Resting-state studies also observed greater FC of the IFG and other networks (e.g., DMN) in more highly creative individuals (Beaty RE, M Benedek, et al. 2014; Beaty RE, PJ Silvia, et al. 2014).

Consistent with these findings, previous studies have observed increased activation of the MTG during DTTs (Kleibeuker SW et al. 2013; Kleibeuker SW et al. 2017). The IFG and left MTG belong to the semantic system (Foster NL et al. 2005; Binder JR et al. 2009). The function of the IFG is the retrieval and selection of relevant remote associations (Benedek M, R Beaty, et al. 2014; Benedek M, E Jauk, et al. 2014), while the MTG is associated with the activation of long-term memory (Martin A 2001), which is closely implicated in the creative idea generation process (Fink A et al. 2009; Abraham A 2014). Thus, highly creative individuals have a more flexible semantic associative network, as reflected by the large entropy values of the IFG and MTG.

Furthermore, in previous studies, patients with schizophrenia exhibited high entropy values at the mean whole-brain level (particularly in the frontal lobe), which also partially support our results. A close relationship between psychiatric disorders (particularly schizophrenia) and creativity has been identified. For example, a behavioural study showed that individuals who exhibit greater performance in artistic and creative fields have higher schizotypy scores (GS B et al. 2011). Genetic research has also revealed an association between a creative profession or an artistic society membership and higher polygenic risk scores for schizophrenia, suggesting that creativity and psychosis may share genetic roots (Power RA et al. 2015). Together with the finding that patients with schizophrenia have more complex fMRI signals that are reflected by higher entropy values than healthy controls (Sokunbi MO et al. 2014), our results showing a positive correlation between creativity and regional entropy in the resting brain further support the hypothesis that people with schizophrenia and highly creative individuals share common psychological attributes from the perspective of brain function dynamics.

More importantly, our main results were well replicated in both independent samples from two different cultures. Positive correlations between the total verbal creativity score and regional BEN in the left dACC/pre-SMA and left DLPFC were found in both independent samples, although the correlation between the total score and regional BEN in the left DLPFC was marginally significant in independent sample 1. However, the results were well replicated in independent sample 2, even using a different creativity test. Regarding the three dimensions of verbal creativity, regional BEN in the left DLPFC was positively correlated with originality and flexibility scores in independent sample 1, which is slightly different from our main results that regional BEN in the left DLPFC positively correlated with fluency and flexibility scores. However, the flexibility score consistently correlated with the regional BEN in the left DLPFC in both the discovery and validation datasets. As noted above, the entropy value depicts irregular and variable fluctuations in resting-state brain activity, and the entropy value of the DLPFC may be related to cognitive flexibility, which is associated with creativity (Zabelina DL and MD Robinson 2010; Chen Q et al. 2014). Thus, these findings may explain the robust relationship between the flexibility score and regional entropy value of the left DLPFC.

Finally, the present study has several limitations. First, creativity is a multi-dimensional process, and divergent thinking is a critical indicator of creativity (Runco MA and S Acar 2012). The present study mainly focused on the association between BEN and divergent thinking. However, convergent thinking is also considered an aspect of creativity (Cropley A 2006; Jung RE et al. 2013). Therefore, the current findings should be explained within the context of divergent thinking and researchers designing future studies should considering examining the association between BEN and convergent thinking. Second, BEN is a data-driven voxel-based sample entropy (SampEn) approach. SampEn is largely independent of data length and displays relative consistency over a broader range of possible parameters (Richman JS and JR Moorman 2000). It is also fairly unaffected by low-level noise and is robust to large or small artefacts (Zhang XS and RJ Roy 2001). However, the calculation of SampEn is based on a prespecified distance threshold ($r = 0.6$ in this study), which may have affected the estimated entropy but should not have affected the group-level entropy analysis. Future studies should explore the effects of different thresholds and attempt to identify the optimal threshold for your particular datasets.

CONCLUSION

In summary, our results first identified a robust correlation between verbal creativity and regional BEN in the resting brain and showed that a higher BEN and higher information processing capacity predict higher potential creativity. Specifically, verbal creativity is consistently positively correlated with regional BEN in the left dACC/pre-SMA and left DLPFC, which is involved in cognitive flexibility and inhibitory control. In addition, the three dimensions of verbal creativity (fluency, flexibility and originality scores) positively correlate with regional BEN in the left IFG and left MTG, which indicates a flexible semantic associative network in highly creative individuals. More importantly, the findings were successfully replicated in two different cultural populations, confirming the strength and reliability of our results. In general, these findings provide new insights that improve our understanding of the relationship between the temporal dynamics of the resting brain and verbal creativity.

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Table 1 Descriptive statistics of the demographic and behavioural assessments

	Discovery dataset (N=386)	Independent sample 1 (N=431)	Independent sample 2 (N=132)
Age	20.00 ± 1.16	19.56 ± 1.47	22.67 ±5.99
Sex (M/F)	182/204	119/312	36/96
IQ	65.60 ± 3.96	127.91 ± 8.53	8.74 ±1.89
Originality	45.30 ± 16.40	24.57 ± 10.33	\
Flexibility	26.70 ± 6.30	6.46 ± 2.19	\
Fluency	57.30 ± 18.60	10.62 ± 4.22	\
Total score	129.00 ± 39.30	41.66 ± 16.25	1.70 ±0.27

Table 2 Brain regions in which the regional BEN correlate with verbal creativity

Creativity	Region	Side	Peak coordination (MNI)			Cluster size	
			X	Y	Z	k (voxels)	T-score
Total creativity score							
	dACC/pre-SMA	L	-8	18	54	44	4.99*
	DLPFC	L	-16	40	50	154	3.82*
	IFG_Oper	L	-36	16	34	53	4.48*
	IFG_Tri	L	-56	28	26	66	4.13*

Flexibility score						
dACC/pre-SMA	L	-8	18	54	42	5.12*
DLPFC	L	-16	40	50	197	3.97*
IFG_Oper	L	-36	16	34	53	4.62*
IFG_Tri	L	-56	28	26	76	4.51*
Fluency score						
dACC/pre-SMA	L	-8	18	54	51	4.61*
DLPFC	L	-16	48	34	118	3.72*
IFG_Oper	L	-34	14	36	65	4.75*
MTG	L	-56	-16	-12	38	4.31*
Originality score						
dACC/pre-SMA	L	-8	18	54	28	4.38*
IFG_Oper	L	-38	18	34	27	3.97*

Note: MNI=Montreal Neurological Institute, dACC/pre-SMA=dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC=dorsolateral prefrontal cortex, IFG_Tri=the triangular region of the inferior frontal gyrus, IFG_Oper=the opercular region of the inferior frontal gyrus, MTG=middle temporal gyrus. *Significant levels for correction were set at $P < 0.05$, small-volume corrected.

Captions to figures

Figure 1. Top: regions of positive correlations between regional BEN and total creativity scores. Bottom: scatter plots depicting significant correlations between regional entropy values and total

creativity scores. dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex, IFG_Tri: the triangular region of the inferior frontal gyrus, IFG_Oper: the opercular region of the inferior frontal gyrus.

Figure 2. Top: regions of positive correlations between regional BEN and the three dimensions of verbal creativity (originality/fluency/flexibility scores). Bottom: scatter plots depicting significant correlations between regional entropy values and the three dimensions of verbal creativity (originality/fluency/flexibility scores). dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex, IFG_Tri: the triangular region of the inferior frontal gyrus, IFG_Oper: the opercular region of the inferior frontal gyrus, MTG: middle temporal gyrus.

Figure 3. Scatter plots depicting significant correlations between regional entropy values of the left dACC/pre-SMA and/or DLPFC and creativity scores in independent sample 1 (top: total score, middle: originality score, bottom: flexibility score). dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex.

Figure 4. Scatter plots depicting significant correlations between regional entropy values of the left dACC/pre-SMA and/or DLPFC and creativity score in independent sample 2. dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex.

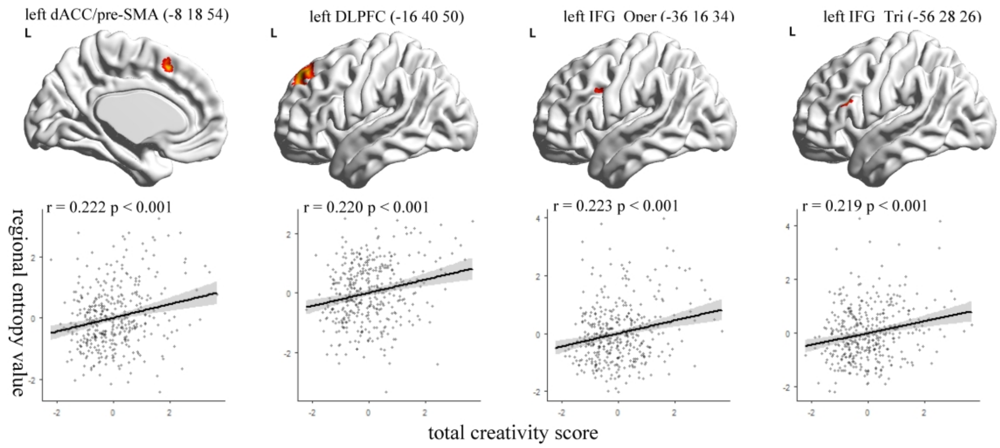

Figure 1. Top: regions of positive correlations between regional BEN and total creativity scores. Bottom: scatter plots depicting significant correlations between regional entropy values and total creativity scores. dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex, IFG_Tri: the triangular region of the inferior frontal gyrus, IFG_Oper: the opercular region of the inferior frontal gyrus.

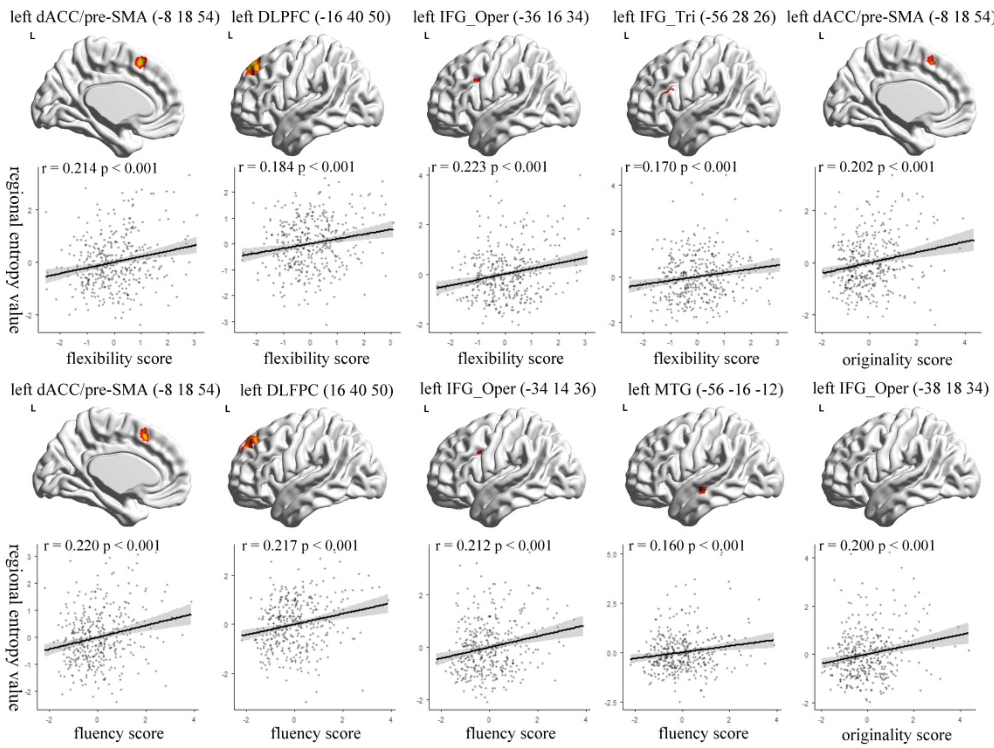

Figure 2. Top: regions of positive correlations between regional BEN and the three dimensions of verbal creativity (originality/fluency/flexibility scores). Bottom: scatter plots depicting significant correlations between regional entropy values and the three dimensions of verbal creativity (originality/fluency/flexibility scores). dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex, IFG_Tri: the triangular region of the inferior frontal gyrus, IFG_Oper: the opercular region of the inferior frontal gyrus, MTG: middle temporal gyrus.

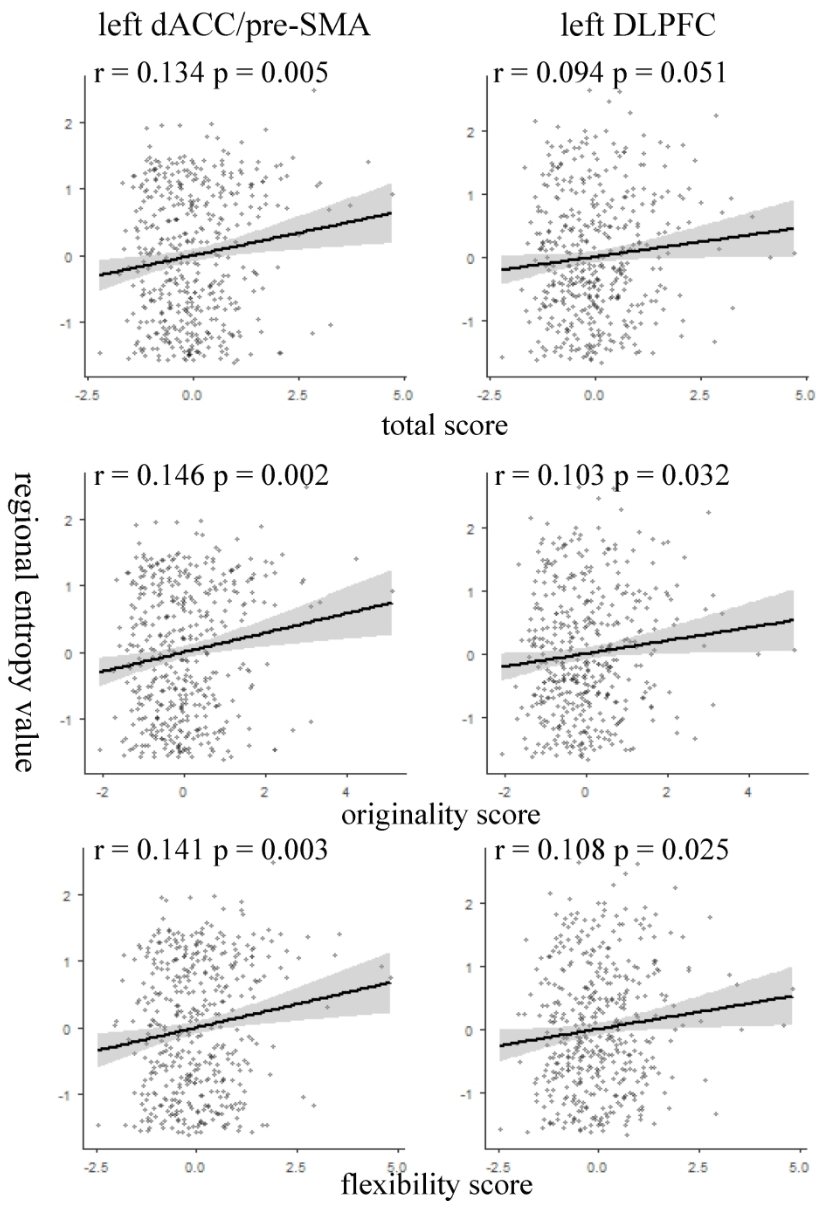

Figure 3. Scatter plots depicting significant correlations between regional entropy values of the left dACC/pre-SMA and/or DLPFC and creativity scores in independent sample 1 (top: total score, middle: originality score, bottom: flexibility score). dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex.

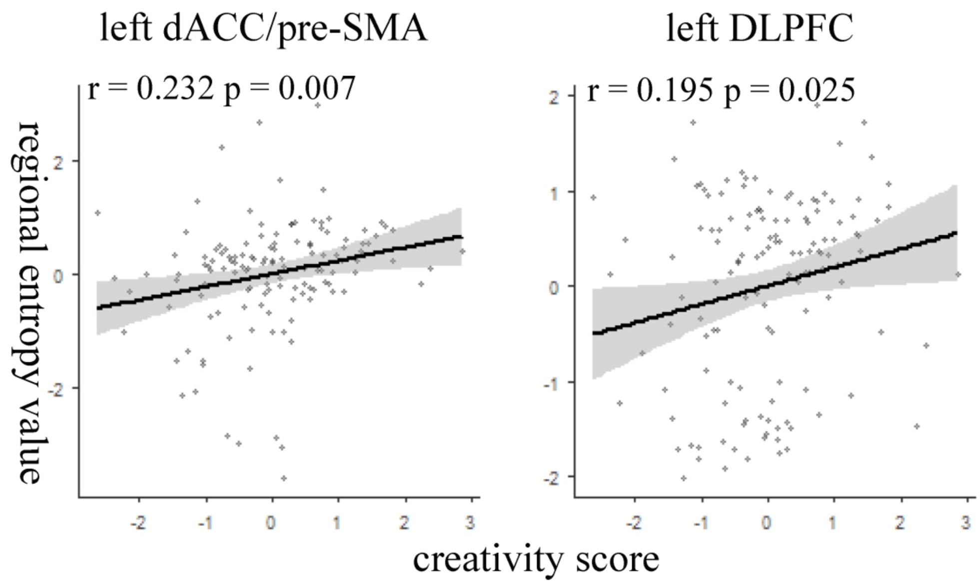

Figure 4. Scatter plots depicting significant correlations between regional entropy values of the left dACC/pre-SMA and/or DLPFC and creativity score in independent sample 2. dACC/pre-SMA: dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC: dorsolateral prefrontal cortex.

SI Materials and Methods

Independent Sample 1

Participants

Originally, 684 subjects from the Gene-Brain-Behavior project of Southwest University were included in independent sample 1. The subjects were all right-handed and completed the verbal creativity test. Two hundred fifty-three subjects were excluded, of whom 80 were excluded due to inconsistent creativity ratings, one subject was excluded due to the lack of brain imaging data, and 172 subjects were excluded due to missing intelligence data. These exclusions resulted in a final sample of 431 subjects (119 males) aged 16-26 years (mean ± SD = 19.56 ± 1.47); all of these subjects completed the behavioural tests and brain imaging data acquisition.

Assessment of Verbal Creativity

The verbal creativity test administered to participants in independent sample 1 was the fourth task of the verbal form of the TTCT (Torrance EP 1974). This task required subjects to improve a product (toy elephant) by proposing creative ideas for 10 minutes. The total score was the sum of the fluency, flexibility, and originality scores for this task. Each dimension of creativity was highly correlated with the total score and the other scores in the discovery dataset (all r values > 0.8, Table S1).

Assessment of General Intelligence

The intelligence test administered to participants in independent sample 1 was the Chinese version of the Wechsler Adult Intelligence Scale (WAIS–RC) (Gong, 1992). It consists of a battery of subtests (vocabulary, arithmetic, digit span, similarities, picture completion, information, comprehension, block design, digit symbol, object assembly, and picture arrangement). For a thorough description of these subtests, please see the study published by Wechsler and colleagues (Wechsler D and MM De Lemos 1981). These subtests were administered individually and then computed to measure verbal (VIQ) and performance (PIQ) intelligence. A complete IQ score, which is the combination of the VIQ and PIQ scores, was used in the validation analysis. This scale showed adequate reliability and has been widely used in China (Yao *et al*., 2004; Zhao *et al*., 2014).

MRI Data Acquisition, Preprocessing and BEN Mapping

The MRI data acquisition parameters, preprocessing and BEN mapping procedures were the same as the main discovery dataset.

Independent Sample 2

Participants

One hundred sixty-three students from the University of North Carolina at Greensboro (UNCG) comprised independent sample 2. All subjects had normal or corrected-to-normal vision and reported no history of neurological disorders. Seven subjects were excluded due to missing age and sex information, one subject was excluded due to a missing intelligence score, and 23 subjects were excluded due to errors in the brain imaging analysis, thus resulting in a final sample of 132 subjects (36 males, mean age = 22.67 years, SD = 5.99).

Assessment of Verbal Creativity

The verbal creativity tests administered to the participants independent sample 2 consisted of an in-scanner alternative use task (AUT) and two postscan AUTs. Subjects were required to think of novel and useful uses for common objects in the AUT. For the in-scanner AUT, the task paradigm consisted of a jittered fixation cross (4-6 s), a cue that indicated the task requirement ('create' or 'object', 3 s), a thinking period when an object in text (e.g., 'umbrella') was presented, and a verbal response period requiring subjects to report their most creative answer into an MRI-compatible microphone (5 s). These answers were recorded by an experimenter for a subsequent idea quality analysis. In the postscan AUTs, participants were required to continuously generate alternate uses for each of two objects ('box' and 'rope'; 2 minutes each). Subsequently, four trained raters were recruited to evaluate the creative quality of these responses for both in-scanner AUT and postscan AUTs using a scale ranging from 1 (not at all creative) to 5 (very creative) points (Silvia PJ et al. 2008). Finally, the average of the two creativity scores from the in-scanner AUT and the postscan AUTs was used in the validation analysis. For a thorough description of the AUT, please see the study by Beaty et al. (2018).

Assessment of General Intelligence

The intelligence tests administered to the participants in independent sample 2 included three tasks from the Cattell Culture Fair Intelligence Test (CFIT): number series, letter sets and the matrices task. The number series task required subjects to complete a series of numbers by discovering a guiding rule (15 items, 4.5 minutes) (Thurstone LL 1938). The letter sets task required subjects to choose which set does not follow the rule guiding the other four sets when facing a series of four-letter combinations (16 items, 4 minutes) (Ekstrom RB et al. 1976). The matrices task from the CFIT required subjects to choose the missing part of a matrix to complete the figure pattern (13 items, 3 minutes) (Cattell RB and A Cattell 1960). All tasks were administered electronically using MediaLab.

MRI Data Acquisition

MRI data were acquired using a 3 T Siemens Magnetom MRI system (Siemens Medical Systems) with a 16 channel head coil. One hundred fifty images (five minutes) were obtained using a gradient echo-planar imaging sequence: TR = 2000 ms, TE = 30 ms, slices = 32, flip angle = 78°, FOV = 192 × 192 mm^2, and voxel size = 3.5 × 3.5 × 4 mm^3. Following functional imaging, a high-resolution T1 scan (TR = 2350 ms, TE = 2.26 ms, FOV = 256 x 256 mm^2, slice thickness = 1 mm, voxel size = 1 mm isotropic) was acquired for anatomical normalization.

Image Preprocessing and BEN Mapping

The data preprocessing and BEN mapping procedures were the same as used in the main discovery dataset.

Table S1 Correlation of creativity scores between discovery dataset and independent sample 1

Discovery dataset (N=386)	Independent sample 1 (N=431)			
	Originality	Flexibility	Fluency	Total score
Originality	\	0.896 (<0.001)	0.904 (<0.001)	0.991 (<0.001)
Flexibility	0.802 (<0.001)	\	0.836(<0.001)	0.921 (<0.001)

Fluency	0.875 (<0.001)	0.829 (<0.001)	\	0.947 (<0.001)
Total score	0.959 (<0.001)	0.886 (<0.001)	0.970 (<0.001)	\

Table S2 Brain regions in which the regional BEN correlate with verbal creativity in the combined sample

Creativity	Region	Side	Peak coordination (MNI)			Cluster size	
			X	Y	Z	k (voxels)	T-score
Total creativity score							
	dACC/pre-SMA	L	-12	50	2	36	3.90*
	DLPFC	L	-8	42	20	28	4.11*
Fluency score							
	DLPFC	L	-8	42	20	74	4.48*
Originality score							
	dACC/pre-SMA	L	-8	18	54	28	4.38*
	DLPFC	L	-8	42	18	38	4.37*
	IFG	L	-54	34	-4	105	3.83*
	IFG	R	32	32	-20	24	3.94*

Note: MNI=Montreal Neurological Institute, dACC/pre-SMA=dorsal anterior cingulate cortex\pre-supplementary motor area, DLPFC=dorsolateral prefrontal cortex, IFG = inferior frontal gyrus. *Significant levels for correction were set at $P < 0.05$, small-volume corrected.

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