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Functional lateralization of the medial temporal lobe in novel associative processing during creativity evaluation

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Abstract

Although hemispheric lateralization of creativity has been a longstanding topic of debate, the underlying neurocognitive mechanism remains poorly understood. Here we designed 2 types of novel stimuli—"novel useful and novel useless," adapted from "familiar useful" designs taken from daily life—to demonstrate how the left and right medial temporal lobe (MTL) respond to novel designs of different usefulness. Taking the "familiar useful" design as a baseline, we found that the right MTL showed increased activation in response to "novel useful" designs, followed by "novel useless" ones, while the left MTL only showed increased activation in response to "novel useful" designs. Calculating an asymmetry index suggests that usefulness processing is predominant in the left MTL, whereas the right MTL is predominantly involved in novelty processing. Moreover, the left parahippocampal gyrus (PHG) showed stronger functional connectivity with the anterior cingulate cortex when responding to "novel useless" designs. In contrast, the right PHG showed stronger connectivity with the amygdala, midbrain, and hippocampus. Critically, multivoxel representational similarity analyses revealed that the left MTL was more effective than the right MTL at distinguishing the usefulness differences in novel stimuli, while representational patterns in the left PHG positively predicted the post-behavior evaluation of "truly creative" products. These findings suggest an apparent dissociation of the left and right MTL in integrating the novelty and usefulness information and novel associative processing during creativity evaluation, respectively. Our results provide novel insights into a longstanding and controversial question in creativity research by demonstrating functional lateralization of the MTL in processing novel associations.

Key words: medial temporal lobe; hippocampus; hemispheric lateralization; creativity; fMRI.

Introduction

Creativity, conceptualized as generating original (novel) and valuable (useful) thoughts (Barron 1955; Runco and Charles 1993; Sternberg and Lubart 1996; Hennessey and Amabile 2010; Runco and Jaeger 2012), is a critical factor in technological development and social progress. However, the brain basis of creativity is still poorly understood. Since Sperry's "left and right brain division theory" (Sperry 1974), a strong role of the right hemisphere for creativity has been discussed in particular popular science; however, also a considerable body of empirical evidence suggests hemispheric asymmetries in creativity processing (Rubenzer 1979; Torrance 1982; Bowden and Beeman 1998; Beeman et al. 2000; Bowden and Jung-Beeman 2003; Lindell 2011; Beeman and Chiarello 2013; Huang et al. 2013; Duboc et al. 2015; Mayseless and Shamay-Tsoory 2015; Chen et al. 2019). Evidence for a distinctive role of the right hemisphere for creativity stems from split-brain research (Sperry 1974; Gazzaniga 2005) and is also supported by behavioral studies, which showed that semantic activation in the right hemisphere benefitted creative problem-solving (Beeman et al. 2000; Lindell 2011; Beeman and Chiarello 2013; Huang et al. 2013; Mayseless and Shamay-Tsoory 2015; Chen et al. 2019). Similarly, brain lesion studies showed that right hemispheric damage can lead to difficulty drawing inferences (Beeman et al. 1994, 2000) and understanding metaphoric or connotative meanings (Mashal et al. 2005; Mashal and Faust 2008; Beaty and Silvia 2013).

More recently, neuroimaging studies have linked different processes of creativity with the right hemisphere:

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artistic creativity (Seeley et al. 2008; Fink et al. 2009; Mayseless et al. 2014), remote associates (Luft et al. 2018), and insight problem-solving (Bowden and Jung-Beeman 2003; Luo and Niki 2003; Zhao et al. 2014). While a meta-analysis has found evidence for a relative dominance of the right hemisphere during creative thinking (Mihov et al. 2010), overly simplistic views on creativity lateralization have been criticized (Corballis 2018), and different kinds of creative processes appear to differ in their lateralization (Boccia et al. 2015). Accumulating evidence suggests that creativity is a high-level cognitive process based on primary cognitive functions such as memory, attention, and cognitive control (Boccia et al. 2015). Accordingly, it is plausible that creativity is not an exclusive domain of the right hemisphere but also involves the interaction and integration of information from both hemispheres (Beaty et al. 2016, 2018, 2020; Boot et al. 2017; Benedek and Fink 2019).

The two-fold model of creativity proposes that creativity has two processes: a "generation" process and an "evaluation" process (Ellamil et al. 2012; Finke et al. 1992; Kleinmintz et al. 2019; Min et al. 1982; Sowden et al. 2015). New ideas are produced through the free association of remote concepts during the "generation" process. In contrast, the "value, effectiveness, usefulness," and "novelty" of the generated ideas are evaluated during the "evaluation" process to detect the genuinely creative ideas (Martindale 1999; Ellamil et al. 2012; Mayseless et al. 2014). Within this framework, the right hemisphere is mainly associated with the generation (Bowden and Beeman 1998; Seeley et al. 2008; Huang et al. 2021), and the left hemisphere is primarily related to the evaluation of creative content (Mayseless et al. 2014; Rémi et al. 2015).

Recently, multiple studies have shown that the "evaluation" process is essential for creativity (Runco and Charles 1993; Kumaran and Maguire 2009; Runco and Jaeger 2012). In this process, an idea's "relevance, value," and "novelty" are accessed, retrieved, analyzed, and integrated from memory. A too stringent evaluation process may inhibit the generation of new ideas, while a too lenient evaluation process may lead to increased adoption of "useless" or "inappropriate" ideas (Ellamil et al. 2012; Mayseless et al. 2014; Kleinmintz et al. 2019). In the left hemisphere, balancing objective and reasonable evaluation criteria (standards that most people accept and can lead to better creative performance) may allow novel ideas to be produced by discarding trivial or useless ideas (Dailey and Mumford 2006; Mayseless et al. 2014). Clinical research has frequently reported the emergence of artistic creativity following degenerative brain damage in the left hemisphere (Miller et al. 1996; Miller and Hou 2004; Seeley et al. 2008; Mayseless et al. 2014), which supports the notion of lateralization of creative evaluation/inhibition control in the left hemisphere. For example, a patient with Parkinson's disease reported increased artistic production with suppressive deep brain stimulation of the left hemisphere (Drago et al. 2009). Another patient with severe degeneration of the left inferior frontal cortex showed increased figural creativity (Seeley et al. 2008). In other words, it appears that damage in some regions of the left hemisphere can remove the inhibition exerted on the right hemisphere of the brain—which then, in turn, experiences greater freedom and flexibility to promote "remote" or "impossible" associations (Mayseless et al. 2014). It is, therefore, possible that the evaluation process associated with the executive control system—predominantly associated with the left hemisphere—can impose an inhibitory effect on the creative generation process, restraining and hindering ideas, and associative processing (Mayseless et al. 2014).

Although all of these studies provide insights into the hemispheric lateralization of creativity, several questions remain open. Firstly, considering that "novelty" and "usefulness" are the two defining features of creativity (Runco 2004; Hennessey and Amabile 2010; Runco and Jaeger 2012; Ren, Huang, et al. 2020a), the neural mechanisms of the hemispheric functional differences in creativity processing based on "novelty" and "usefulness" features still remain under-specified.

Secondly, the hemispheric differences of creativity under natural conditions remain unclear. The current study applies no intervention to the information input (such as no constricting the visual field), leading to a more natural condition for creativity and higher external validity. Previous studies mainly involved controlling the information received by the left and right hemispheres through specific restrictions, including research such as "split-brain" studies, brain lesion studies, and the use of "field of view with hemisphere crossing" to control the information presented in a unilateral hemisphere. However, when real-life creative ideas do arise, there is likely competition between the left and right hemispheres in a healthy brain—as opposed to laboratory experiment—which artificially shields one hemisphere from incoming information and thus prevents that hemisphere from participating in any subsequent bilateral evaluation process.

Lastly, previous studies have generally focused on the functional difference between the left and right hemispheres but did not investigate differences in specific creativity-related brain regions, such as the medial temporal lobe (MTL). Several studies suggest that the MTL is a central region involved in creativity and plays an essential role in processing both novelty and usefulness information (Luo and Niki 2003; Wixted and Squire 2011; Palombo et al. 2015; Ren, Huang, et al. 2020a). The MTL is involved in novelty detection (Blackford et al. 2010; Kafkas and Montaldi 2014), novel associations (Kohler et al. 2005; Kumaran and Maguire 2009; van Kesteren et al. 2012), and forming of new memories (Eichenbaum et al. 2007; Squire et al. 2007; Shohamy and Wagner 2008; Wixted and Squire 2011). Additionally, the MTL is involved in task-related processes that are relevant to goal-directed task activity (Backus et al. 2016) in addition to insight (Luo and Niki 2003) and usefulness processes

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(Huang et al. 2015, 2018). Moreover, the MTL is part of the default mode network (DMN)—for which a growing body of evidence suggests a central role in creativity and idea generation via coupling within the executive network (Beaty et al. 2015, 2016; Liu et al. 2015; Fox and Beaty 2019).

Furthermore, many studies have shown the different functionality of the left and right MTL (Strange et al. 1999; Monchi et al. 2001; Burgess et al. 2002; Cohn-Sheehy et al. 2021). Previous studies showed that the left MTL appears particularly involved in meaningful (as opposed to nonsense) or verbal/semantic-related novel stimuli (Strange et al. 1999), the task-related novel association (Qin et al. 2007, 2009), processing the unexpectedness/uncertainty (Richardson et al. 2004; Harrison et al. 2006), and context-dependent episodic or autobiographical memory (Burgess et al. 2002). The right MTL is more responsive to novel objects and spatial scenes (Burgess et al. 2002; Luo and Niki 2003; Mayseless et al. 2014) and memory for locations within an environment (Burgess et al. 2002). Beyond the functional difference between left and right MTL, a left lateralization of the executive control system (Wagner et al. 2001; Hirose et al. 2012; Huang et al. 2021) may also cause functional lateralization in creativity processing. For example, previous studies showed that left hemisphere activation inhibits the production of novel ideas (Seeley et al. 2008; Mayseless and Shamay-Tsoory 2015; Rémi et al. 2015; Luft et al. 2018). The executive control system might therefore affect the functional differences between left and right MTL in its critical role of novel ideas production (Luo and Niki 2003; Duff et al. 2013; Mack et al. 2016; Cabeza et al. 2020; Thakral et al. 2020; Zhang et al. 2020; Ren, Huang, et al. 2020a).

In the present study, we used event-related functional magnetic resonance imaging (fMRI) to investigate the creativity evaluation mechanism in the left and right hemispheres. We used 3 stimuli through which we could separate novelty and usefulness. There were 2 kinds of novel conditions: one was high in both novelty and usefulness, called the "novel useful" (NU) condition; the other was novel but useless, called "novel useless" (NS) condition. As a baseline, we used familiar stimuli, which are low in novelty but high in usefulness, the "familiar useful" (FU) condition. Our 2 novel conditions were constructed by making changes to ordinary products: appropriate changes made them into NU products and inappropriate changes made them into NS products. We investigated the response of the left and right brain regions to novel stimuli with different usefulness to evaluate to which degree the evaluation criteria (lenient/stringent) are localized in left and right brain regions.

Considering the essential role of the MTL in both novelty and usefulness information processing, we hypothesized that the left and right MTL have different functions in response to the novel stimuli: the right MTL has a more lenient evaluation criterion in the creative evaluation process and is mainly involved in novelty processing. In contrast, the evaluation criteria for the left MTL are stricter, and it is therefore mainly involved in the usefulness processing. Taken together, we suggest that creativity relies on the cooperation of both hemispheres.

Methods

Research transparency and openness

The MRI raw data, study materials, and experimental program were acquired from the Open Science Framework (https://osf.io/n9cy7) (Ren, Zhou, et al. 2020b), an ongoing project exploring the cognitive brain mechanisms mediating the processing of usefulness and novelty features in creative thinking (Huang et al. 2015; Huang et al. 2018; Ren, Huang, et al. 2020a). The full details regarding the data preprocessing and stimuli standardization were described in a previous publication (Ren, Huang, et al. 2020a).

Research significance and difference from our previous study

In the current study, we significantly expanded upon our previous hypothesis, to investigate the extent to which functional lateralization in the MTL can account for these findings, since previous studies have suggested that left and right MTL regions are asymmetrically involved in different memory stages and mnemonic materials (Tulving et al. 1994; Nyberg, McIntosh, Cabeza, et al. 1996a; Nyberg, McLntosh, Houle, et al. 1996b; Martin 1999; Golby et al. 2001; Dalton et al. 2016). As a growing number of studies have showed that memory shares common neural networks with creativity, especially in the MTL (Madore et al. 2017; Beaty et al. 2018), it is necessary to investigate the role of the lateralization of MTL function in the creativity processing, which has so far never been tested. The current study focused on an entirely new research question, tested different research hypotheses, and presented different analytical approach ideas from the previous study (detail in Supplementary Material). All content in this paper is original, and no results overlap with the previous article (Ren, Huang, et al. 2020a).

Participants

Twenty-one undergraduates or graduate students (10 females, mean age ± SD, 22.10 ± 2.05) were recruited as paid volunteers in this study. All the participants were native Chinese speakers, right-handed, had a standard or corrected-to-normal vision, and had no history of neurologically or psychiatric disease. Two participants (2 males) were excluded from the fMRI analysis (one was reported headache during scanning, and the other had excessive head motion during scanning). Informed consent was obtained from each participant by a protocol approved by the ethics committees of the Center for Biomedical Imaging Research, Tsinghua University.

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Materials and procedures

We used 153 product pictures selected from a broader set of more than 300 pictures. Each product picture was presented with an interpretative sentence, including the products' name and critical function (11–12 words). The selected pictures contained 3 kinds of stimuli, with 51 items in each condition. The FU product was the baseline in this study, a typical product that individuals often encounter and use in their daily lives. For example, an umbrella, with the following description "an umbrella that can be used to prevent a person from getting wet." The other 2 types of products were the creative stimuli with different usefulness: The NS products were novel but with low usefulness, which were made by a novel but inappropriate change to the original design. For example, a car tire, with the description "a car tire designed to have six edges and corners," or a writing desk, with the description "a wooden writing desk covered with deadwood cracks." The NU products included a novel and appropriate change that could reasonably extend the function of the ordinary design and make it "truly innovative." For example, a bicycle seat with the caption "a multi-functional bike seat which can be used as a lock," and a toothbrush with the caption "a toothbrush that balances upright, like a tumbler" (Fig. 1A). We standardized the stimuli for novelty, usefulness, complexity, understandability, and the low-level visual features based on a pilot study from 2 independent groups of participants, as reported in Ren, Huang, et al. (2020a).

The experiment procedures consisted of 4 phases: the experimental practice phase, MRI scanning phase, fMRI scanning phase, and post-scan test phase. In the experimental practice phase, participants were familiarized with the experimental procedures by completing 15 trials (5 min). In the MRI scanning phase, T1 images were acquired for each participant during eyes closed (8 min). During the fMRI scanning phase, participants completed 153 trials equally divided into 3 runs and 3 conditions, with 17 trials per condition for each run that included 3 conditions. The order of the trials was pseudo-randomized with the constraint that the same condition trials could not appear more than 3 times in each run, and the sequence of 3 runs was balanced across all participants. Each picture and interpretive text appeared for 6 s. The participants were asked to focus on thoroughly understanding the displayed designs and evaluate whether the design was useful (Yes/No) by pressing a button using the index and middle fingers of the right hand within 6 s. The "usefulness" evaluation was chosen rather than the novelty evaluation because it is a more natural task and overlaps with comprehending the design. This task ensured that participants' attention was focused on understanding the creative design, and as such, their performance in this task could be regarded as an index of their concentration. The resting intervals between trials were randomly jittered 3–5 s. The duration of each run was 9 min 35 s, and the entire fMRI session took 36 min 45 s. There was 1-min resting interval between each run. In the post-scan test phase, participants were asked to rate the degree of novelty and usefulness for each of the 153 items they evaluated in the scanner on a 5-point scale (from "1" very low to "5" very high) (Fig. 1B). This study performed 2 methods of fMRI analyses based on different aims. For the univariate general linear model (GLM) analysis, we aimed to investigate hemispheric differences to evaluate novelty versus usefulness within the MTL. Although the stimulus we used was well standardized, there were subtle differences between each subject's novelty and usefulness evaluation. To resolve this potential issue, we excluded items in which participants made different judgments to our definitions to ensure that only trials that meet the novelty and usefulness definition, in general and for the specific participant, are included. The exclusion criteria individually for each participant are as follows: pictures for FU (novelty score > 3 or usefulness score < 3), NS (novelty score < 3 or usefulness score > 3), and NU (novelty score < 3 or usefulness score < 3). The means of remaining items were 49 (44–51, SD = 1.701) for FU conditions, 43 (28–50, SD = 5.943) for NS conditions, and 43 (27–50, SD = 5.858) for NU condition. These remaining items were used for the univariate GLM analysis. For the multivoxel pattern similarity analysis, we aimed to assess the neural representational pattern differences between the left and right MTL in representing items among the 3 conditions and within each condition. As the neural representational pattern difference was sensitive for different items, we modeled all the items for the multivoxel pattern similarity analysis. In addition, we performed the prediction analysis to test the relationship between the brain (neural pattern similarity) and the behavioral rating (post-scan novelty and creativity evaluation).

Imaging data acquisition

Imaging data were collected using a 32-channel head coil on a 3T Philips Achieva 3.0T TX MRI scanner at the Center for Biomedical Imaging Research, Tsinghua University. High-resolution structural T1*-weighted anatomical images of the whole brain were acquired using a 3D gradient-echo pulse sequence (time repetition [TR] = 7.65 ms, echo time [TE] = 3.73 ms, flip angle [FA] = 8°, field of view [FOV] = 230×230 mm, voxel size = $1 \times 1 \times 1$ mm^3, 1 mm thickness). T2*-weighted function images were acquired using a gradient-echo echo-planar sequence based on blood oxygenation level-dependent contrast with the following parameters: TR = 2,000 ms, TE = 35 ms, FA = 90°, FOV = 200×200 mm, 64×64 matrix, voxel size = $3.12 \times 3.12 \times 4$ mm^3, 30 slices, 4 mm thickness.

Imaging data preprocessing

The imaging data preprocessing and analysis were performed with custom scripts combined with core functions from the Statistical Parametric Mapping software

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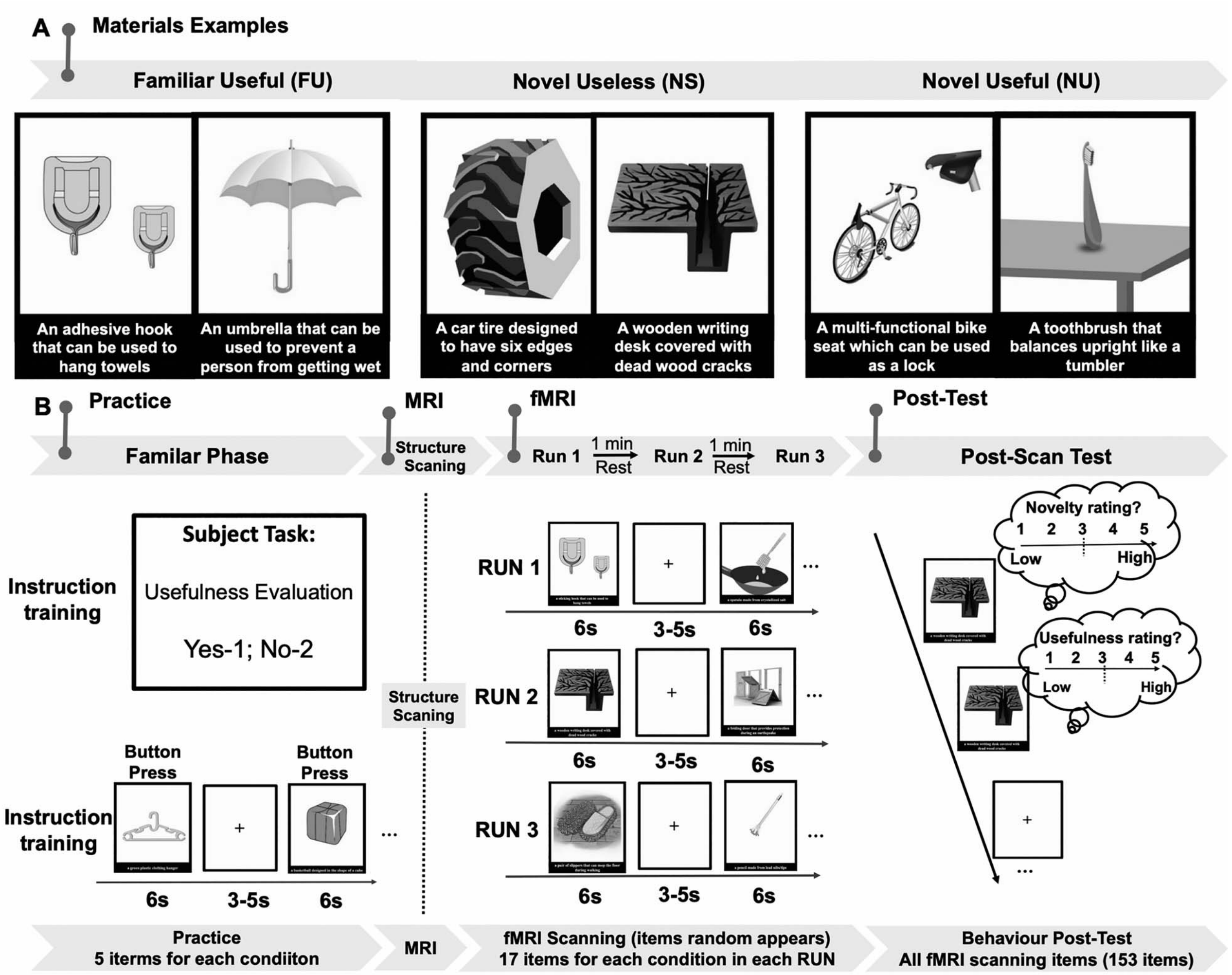

Fig. 1. Material and experimental procedure. A) Materials examples. The FU designs, such as the "adhesive hook" and "umbrella," were the familiar products from daily life, with low novelty and high usefulness. The NS products—In which we make a novel but functionally inappropriate changes to the original design—Result in the high novelty features but a loss of its essential function. The NU products, in which we make novel and functionally appropriate changes, could reasonably extend the function of the ordinary design and thus make it the "truly innovative," with high novelty and high usefulness. B) Experimental procedure. The experiment procedures consisted of 4 phases: The experimental practice phase, MRI scanning phase, fMRI scanning phase (including 3 runs), and post-scan test phase. The experimental practice phase was set for participants to familiarize the experimental procedures before entering the scanner. The MRI scanning phase took about 8 min to acquire the T1 image for each participant while their eyes were closed. The fMRI scanning phase required participants to perform a total of 153 trials, equally divided into 3 runs, with 17 trials per condition each run. In one trial, each picture with the interpretive text appeared for 6 s, and the participants were asked to evaluate whether the product or design was useful or not by pressing a button using the index and middle fingers of the right hand within 6 s. the resting interval between trails was randomly jittered 3–5 s. there was a 1-min resting interval between the 2 runs. The post-scan test phase was asked participants to rate the degree of novelty and usefulness for each of the 153 items on a 5-point scale (from "1" very low to "5" very high).

package (SPM8; http://www.fil.ion.ucl.ac.uk/spm) implemented within Matlab2015a (MathWorks, Natick, MA, USA). During preprocessing, the images for each subject were realigned for head motion correction, corrected for slice timing, spatially normalized to the standard Montreal Neurological Institute (MNI) template, resampled into 2-mm isotropic voxels, and smoothed by convolving an isotropic 3-dimensional Gaussian kernel with a full-width at half-maximum of 6 mm.

Univariate GLM analysis

For the first-level analysis, the data were analyzed using GLMs (Friston et al. 1995). First, the 3 interest regressors of the 3 experimental conditions (FU, NS, and NU) and one no interest regressor including the incorrect items (inconsistent with the original definition) or missed response trials were modeled and convolved with the canonical hemodynamic response function (HRF) for each subject in the first-level analysis. Next, each subject's 6 motion parameters (3 rigid-body translations and 3 rotations) were included to regress out the effects of head movement-related variability. All events were time-locked to the onset of the picture display, and the duration was set to 6 s of the image display. Regionally specific condition effects were tested using linear contrasts for each critical event relative to the baseline and each participant.

The resulting contrast parameter estimates from the individual-subject level were submitted to a random-effect model for a second-level analysis. At the second

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level, we first used a 1-way within-subjects analysis of variance (ANOVA) with *T* contrasts (NU-FU) to investigate the difference between the left and right sides of the targeted regions in the novelty processing. Then, we used a 1-way within-subjects ANOVA with *T* contrasts (NU-NS) to investigate the difference between the left and right sides of the targeted regions in usefulness processing. Next, we performed a conjunction analysis between the novelty effect (NU-FU) and usefulness effect (NU-NS) to investigate the neural activity difference between the left and right sides of the targeted regions associated with novelty and usefulness.

Given our clear hypothesis regarding the MTL across both hemispheres, 4 separate anatomical regions of interest (ROIs) were created, including the left hippocampus (HIP), right HIP, left parahippocampal gyrus (PHG), and right PHG. For this purpose, the 4 anatomical ROIs were created using WFU PickAtlas (Maldjian et al. 2003) (Version3.0; http://www.nitrc.org/projects/wfu_pickatlas) and then used as masks for the small volume correction (SVC) in all the contrast above. Significant clusters for each ROI were identified from the second-level analysis, initially determined using conservative and well-accepted statistical criteria a threshold of the voxel level $P < 0.001$(uncorrected), and then combined a threshold of the cluster-level $P < 0.05$ with family-wise error (FWE) corrections for multiple comparisons. The activation clusters that involve more than 10 voxels are reported to exclude small clusters that are hard to interpret.

fMRI time series analysis

We conducted an fMRI time series analysis of the previous 4 ROIs among the 3 conditions (NU, NS, and FU) to compare the difference between left and right MTL in processing different novel stimuli. fMRI time series is the best way to visualize the signal change based on time among the 3 conditions; it allows us to observe the complete response of the stimuli. First, we performed an fMRI time series analysis with the data from the first-level analysis, in which a univariate GLM composed of 3 separate regressors of interest was modeled and convolved with the canonical HRF for each subject to simulate the HRF-based signal changes across the 3 experimental conditions (FU, NS, and NU). All the onsets within the same condition were averaged, producing one HRF for a specific period. Next, the percentage signal changes within the 4 ROIs were further averaged across all participants to produce a mean percentage or grand average finite impulse response (FIR) time course that lasted for 24 s after the onset of the event. The time series analysis was set to 24 s for display purposes. For an HRF, a stimulus generally needs 3–5 s for a response, with the whole HRF taking approximately 20 s (Gur et al. 2007; Grinband et al. 2008), and HRFs are also varied based on different stimuli (Wang et al. 2021). We chose 24 s to describe the complete HRFs across the 3 conditions, which the similar time also used in the previous publication (Huang et al. 2015). The 4 ROIs were defined by superimposing the activated clusters derived from the conjunction analysis with the anatomical ROIs were defined using WFU Pick-Atlas. Parameter estimates (percentage signal changes) associated with interest conditions were extracted from the previously defined ROIs at the individual level using MarsBar (http://marsbar.sourceforge.net). Moreover, we combined the HRF in our data to choose three time points 6 s, 8 s, and 10 s. Which meets the criteria: (i) the period includes the maximum value of signal change; (ii) the period includes the most significant difference across the 3 conditions. As the time points 6 s, 8 s, and 10 s better reflect the realistically signal changes, we can easily observe the signal changes more accurately and better reflect the differences in signal changes across different experimental conditions. And then, data in time points 6 s, 8 s, and 10 s of each ROIs for each participant were submitted to the statistical software package SPSS21 (https://www.ibm.com/analytics/spss-statistics-software) to test the differences between the 3 conditions separately on the left and right sides.

Lateralization analysis between left and right MTL

To further investigate whether novelty or usefulness processing was lateralized in the MTLs, we calculated the lateralization coefficients of the left and right MTL regions during the novelty processing (NU-FU) and the usefulness processing (NU-NS). We selected the average value for each subject in the 3 time points 6 s, 8 s, and 10 s for the time series of the above-defined ROIs and calculated the asymmetry index (AI) of the left and right MTL regions through the brain AI formula: $AI = (L - R)/(|L| + |R|)$. A positive value indicates lateralization in the left hemisphere, while a negative value would indicate lateralization in the right hemisphere. A near-zero value of AI would indicate a balance between the 2 hemispheres (Chen et al. 2019).

Task-dependent functional connectivity analysis

The PPI analysis investigated why the left and right MTL respond differently to "NS" designs (fMRI time series results), based on the hypothesis that left MTL tends to the stringent criteria and the right MTL tends to the lenient criteria in usefulness evaluation of NS. Here, we hypothesize that stringent criteria in left MTL are due to the stronger functional connectivity between the left MTL and the executive control system. Therefore, we examined the difference between the functional connectivity of the 2 novel conditions (NU vs. NS) via psychophysiological interaction (PPI) analysis (Friston et al. 1997) to investigate the distinct function of left and right MTL in reacting to different levels of usefulness criteria. We separated the PHG region in left and right and defined each ROI as a 6-mm sphere, central at the peak of clusters showing significant activation in conjunction analysis

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(Conjunction: MNI, left PHG peak $x = -30$, $y = -32$, $z = -18$, right PHG peak $x = 36$, $y = -40$, $z = 10$). We performed a generalized form of task-dependent PPI (gPPI) (McLaren et al. 2012) to accommodate more than 2 experimental conditions within the same model. The physiological activity of the 2 seed regions was computed in all voxels of the mean time series and then deconvolved to estimate neural activity. Next, the 4 PPI regressors (FU, NS, NU, and null items) were obtained by multiplying the estimated neuronal activity from the seed region with a vector coding for the effects of each condition to form 4 PPI vectors. The interaction vector was further convolved with a canonical HRF to form 4 PPI regressors of interest. The task condition variable (4 in all, including the item excluding condition) was included in this GLM to remove the effects of the task-related activations.

For second-level group analysis, we focused on the functional connectivity differences between the left and right PHG in usefulness processing with the condition between NU and NS. We have 3 conditions: FU, NS, and NU, but we are only interested in each 2 conditions contrast (*T* contrast) among the 3 conditions. Therefore, we performed a 1-way within-subjects ANOVA with *T* contrast in SPM. The contrast images corresponding to PPI effects at the individual-subject level were then used in a 1-way within-subjects ANOVA with *T* contrast of NS > NU to figure out the process of ROIs-seeded functional connectivity with the NS product (compared to the NU product) to investigate the difference between left and right PHG functional connectivity with other brain voxels in useless novel information. Then, we made another 1-way within-subjects ANOVA with *T* contrast of NU > NS to figure out ROIs-seeded functional connectivity with the NU product (compared to NS product) to investigate the difference between left and right PHG functional connectivity with other brain voxels in useful novel information. Next, a gray matter mask initially masked significant clusters and then determined at a voxel-level on the whole-brain PPI effects using a height threshold of $P < 0.05$ with the false discovery rate (FDR) correction. Additionally, we used uncorrected $P < 0.001$(cluster size > 30) to detect significant amygdala regions where no superthreshold activation was found after FDR correction. Lastly, we also used a SVC ($P < 0.001$ uncorrected at voxel level and $P < 0.05$ FWE corrected at cluster level, cluster >10) in the PPI result with the critical region including the anterior cingulate cortex (ACC), amygdala, midbrain, and HIP. Given our prior hypotheses, these regions may affect lateralization and have different functional connectivity between left and right MTL.

Moreover, as the most crucial difference between left and right MTL is in response to NS designs (fMRI time series analysis), we also compared the left and right PHG functional connectivity with ACC within contrast NS > NU. In a second step, we analyzed regions that are only functionally connected with the right PHG.

Multivoxel pattern similarity analysis

To assess the difference in the neural representational pattern between left and right MTL in representing items among the 3 conditions and within each condition, we performed inter-condition and intra-condition pattern similarity analyses. First, we modeled each item as a separate regressor with a duration of 6.0 seconds using a canonical HRF implemented in SPM8. This resulted in 17 regressors for each condition and 51 regressors in each run (3 runs 153 items in total, each run includes 3 levels, each level has 17 items, the similarity value averaged across the 3 runs). Second, contrast images for each item versus fixation, generated at the individual level analysis within each condition (FU-FU, NS-NS, NU-NU) or across conditions (FU-NU, FU-NS, NU-NS), were then submitted to subsequent intra-condition or inter-condition multivariate pattern similarity analysis. The intra-condition pattern similarity performs the RSA within each condition, which means we compute the similarity trial-by-trial. For each subject, we computed Pearson correlation between each 2 of the items within each condition and obtained $N \times (N-1)/2$ correlation matrices for 3 conditions. Then we averaged each vectorized correlation matrix to get 3 correlation values that represent the similarity of the 3 conditions for this subject. Therefore, we had 3 similarity values for FU, NS, and NU for each subject, respectively. This similarity value represents the degree of pattern similarity within all items of a certain condition. The inter-condition pattern similarity performs the RSA among the 3 conditions, which means we compute the similarity trial-by-trial among the 3 conditions. For example, to calculate the trial-by-trial similarity between NS and NU, we computed the Pearson correlation between each 2 of the items from NS and NU, respectively. We would get the $N \times N$ correlations matrix and average the matrix to get one value representing the similarity between NS and NU for this subject. Therefore, each subject would get 3 similarity values for FU-NS, FU-NU, and NS-NU, respectively.

Next, we implemented a searchlight method to measure inter-condition multivoxel pattern similarity at the whole-brain level (Kriegeskorte et al. 2006, 2008), using a 6-mm spherical region (Etzel et al. 2013) of interest. We extracted the *T* map weights, representing voxel-wise brain activation, estimating the statistically significant value for each item across all conditions from 6-mm spherical ROIs and reshaping them into a single-dimensional vector for each searchlight. Pairwise correlations were then computed among distributed voxels of each searchlight. Next, we computed the inter-condition multivoxel pattern similarity for all conditions within each searchlight. The analysis was then repeated for a searchlight centered on every voxel in the brain. Searchlight maps were separated for cross-item experimental conditions and inter-condition experimental conditions as described above.

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For the ROIs of bilateral hippocampal and bilateral PHG, we used automated anatomical labeling templates as ROIs mask of bilateral MTL (left/right HIP and left/right PHG) to extract the value of the whole-brain searchlight for each of the cross-item and inter-condition experimental conditions. Finally, to better understand the ability of a specific ROI to represent the difference between items within the same condition and the difference between items among the 3 conditions, we determine the dissimilarity score using Fisher's Z transformation of 1 minus the correlation coefficient extract from the whole-brain pattern similarity analysis, separately for each participant (Kriegeskorte et al. 2008; Kriegeskorte and Kievit 2013; Haxby et al. 2014). We compared the difference between left MTL and right MTL inter-condition and intra-condition dissimilarity.

Prediction analysis

The intra-condition pattern similarity values reflect the degree of consistency for neural representation patterns in representing the items in each condition. The similarity between left and right PHG might differ in predicting the post-behavior evaluation for the novel stimuli (NU and NS). We employed a machine learning approach with balanced 4-fold cross-validation to investigate the relationship between the novel stimulus' intra-condition pattern similarity in the left and right PHG and individual changes in usefulness and creativity scores (post-scan test scores). The prediction analysis mitigates the shortcomings of conventional regression models that are sensitive to outliers and have no predictive value (Dubois and Adolphs 2016). The intra-condition pattern similarity score changes in the left or right PHG for each subject in NU (or NS) were entered as an independent variable. Individual changes in the "usefulness" or "creativity" score were entered into a linear regression algorithm as a dependent variable. This measured how well the independent variable predicts the dependent variable, estimated using a balanced 4-fold cross-validation procedure. Data for these 2 variables from all 19 subjects in the fMRI experiment were divided into 4-folds, the linear regression model was established by a leaving-1-fold-out procedure. The final $r_{(\text{predicted, observed})}$ was calculated by averaging the 4 cross-validated folds. Finally, a nonparametric test was used to test the statistical significance of the model, and 1,000 surrogate data sets were generated under the null hypothesis of $\mathrm{r}_{(\text{predicted, observed})}$. The *P*-value was determined by measuring the percentage of generated surrogacy data that was greater than $\mathrm{r}_{(\text{predicted, observed})}$ (Qin et al. 2014; Liu et al. 2016; Yarkoni and Westfall 2017).

Estimates of effect size and post hoc statistical correct

Effect sizes for ANOVAs are partial eta squared, referred to as $\eta_p{}^2$. For the effect sizes of paired *t*-tests, we used Cohen's *d*, which takes the mean difference score as the numerator and the pooled standard deviation from both repeated measures as the denominator (Cohen 2013). Bonferroni correction was applied to control for multiple comparisons.

Results

The MTL region is active in both novelty and usefulness processing

We performed SVC of the 4 ROIs (left/right PHG and left/right HIP) to investigate the activation of the left and right MTL in novelty processing, usefulness processing, and the conjunction of novelty and usefulness. The result showed that both the left and right MTL show significant activation during novelty, usefulness, and the conjunction processing (Supplementary Table S1).

Different activations in the left and right MTL in response to the 2-type novel stimulus

Taking the FIR time course that lasted for 24 s after the onset of the event to compare the left and the right MTL signal change, we found that the signal change in left MTL was significantly highest in the NU condition among the 3 conditions. While in the right MTL, the time-series signal change was showed: the NU is higher than NS and NS is higher than FU.

We also examined the 6 s, 8 s, and 10 s time points to compare the difference of left and right MTL signal change across time with repeated measures ANOVA. There were differences between left and right MTL to respond to the novel stimuli. For the left MTL, the main effect showed at all time points 6 s ($F_{\mathrm{LHIP}}(2, 36) = 21.46, P < 0.001$, $\eta_p{}^2 = 0.54$; $F_{\mathrm{LPHG}}(2, 36) = 31.55, P < 0.001$, $\eta_p{}^2 = 0.64$), 8 s ($F_{\mathrm{LHIP}}(2, 36) = 30.51$, $P < 0.001$, $\eta_p{}^2 = 0.63$, $F_{\mathrm{LPHG}}(2, 36) = 48.66, P < 0.001$, $\eta_p{}^2 = 0.73$), and 10 s ($F_{\mathrm{LHIP}}(2, 36) = 24.52$, $P < 0.001$, $\eta_p{}^2 = 0.58$; $F_{\mathrm{LPHG}}(2, 36) = 31.73, P < 0.001$, $\eta_p{}^2 = 0.64$). Post hoc comparisons showed that the NU was significantly higher than NS ($P_{\mathrm{LHIP6s,8s,10s}} < 0.001$, $P_{\mathrm{LPHG6s,8s,10s}} < 0.001$) and FU ($P_{\mathrm{LHIP6s,8s,10s}} < 0.001$, $P_{\mathrm{LPHG6s,8s,10s}} < 0.001$), but no significant difference between NS and FU ($P_{\mathrm{LHIP6s}} = 0.226$, $P_{\mathrm{LHIP8s}} = 0.624$, $P_{\mathrm{LHIP10s}} = 0.361$; $P_{\mathrm{LPHG6s}} = 0.151$, $P_{\mathrm{LPHG8s}} = 0.125$, $P_{\mathrm{LPHG10s}} = 0.104$). For the right MTL, the main effect was significant at 6 s ($F_{\mathrm{RHIP}}(2, 36) = 18.783, P < 0.001$, $\eta_p{}^2 = 0.511$; $F_{\mathrm{RPHG}}(2, 36) = 20.857, P < 0.001$, $\eta_p{}^2 = 0.537$), 8 s ($F_{\mathrm{RHIP}}(2, 36) = 23.55$, $P < 0.001$, $\eta_p{}^2 = 0.567$, $F_{\mathrm{RPHG}}(2, 36) = 43.02, P < 0.001$, $\eta_p{}^2 = 0.71$), and 10 s ($F_{\mathrm{RHIP}}(2, 36) = 20.76$, $P < 0.001$, $\eta_p{}^2 = 0.536$; $F_{\mathrm{RPHG}}(2, 36) = 33.92, P < 0.001$, $\eta_p{}^2 = 0.65$). Post hoc comparisons showed that NU was significantly higher than NS ($P_{\mathrm{RHIP6s,8s,10s}} < 0.001$, $P_{\mathrm{RPHG6s,8s,10s}} < 0.001$) and FU ($P_{\mathrm{RHIP6s,8s,10s}} < 0.001$, $P_{\mathrm{RPHG6s,8s,10s}} < 0.001$), and NS was significantly higher than FU ($P_{\mathrm{RHIP6s}} < 0.05$, $P_{\mathrm{RHIP8s}} < 0.01$, $P_{\mathrm{RHIP10s}} < 0.05$; $P_{\mathrm{RPHG6s}} < 0.05$, $P_{\mathrm{RPHG8s}} < 0.001$ $P_{\mathrm{RPHG10s}} < 0.01$) (Fig. 2).

The result showed that signal activity in the right MTL responded to novel stimulus even in the low usefulness condition (NU and NS stimulus; signal change NU > NS > FU). However, the left MTL only responded to

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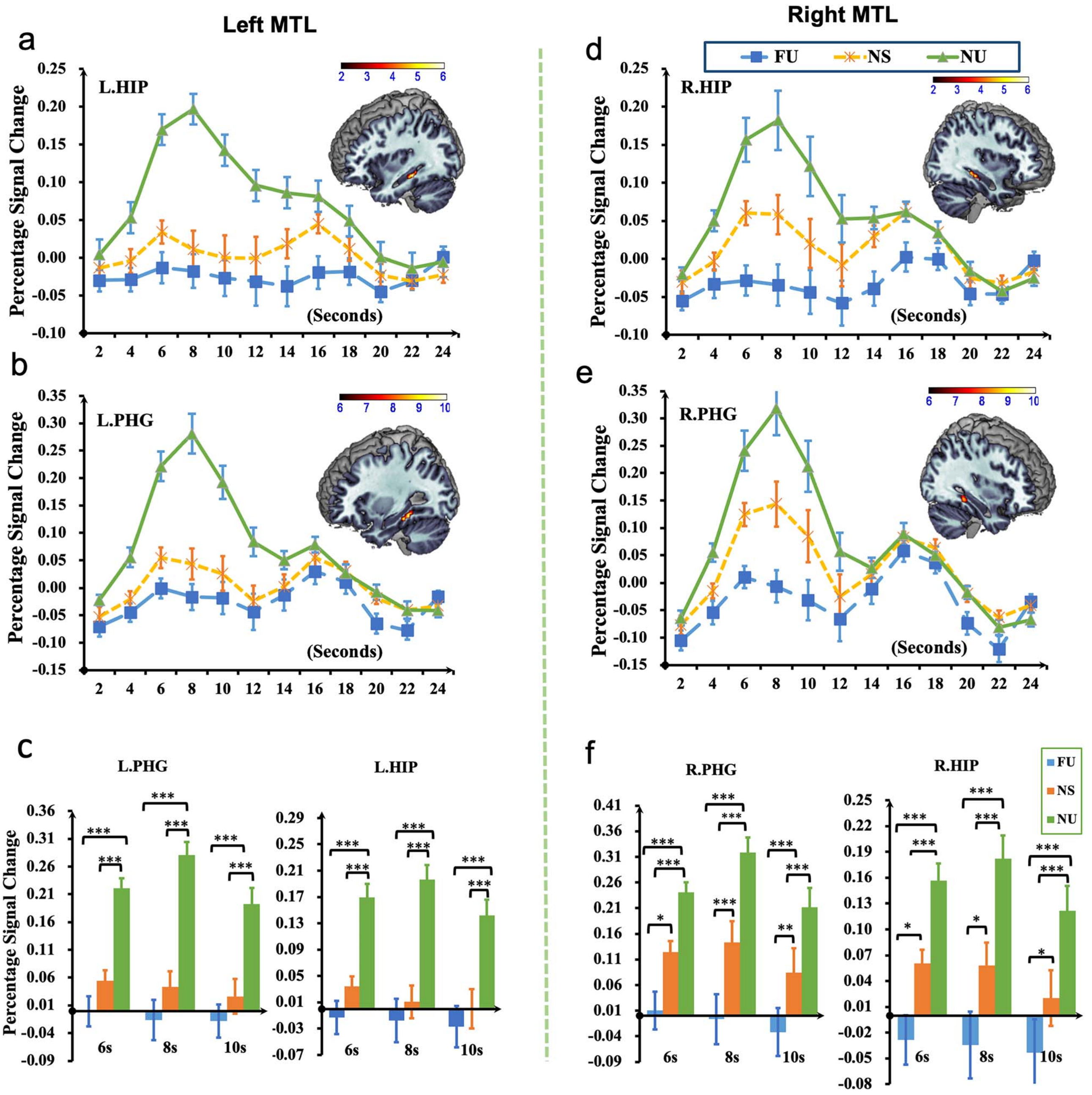

Fig. 2. Time-course of the left and right MTL in response to the 2-type novel stimulus. a, b) The graphs display the time course of the group average signal changes separately for the left MTL (including left HIP and left PHG) and d, e) right MTL. The brain image shows the bilateral parahippocampal and HIP activation in the conjunction analysis of novelty (NU > FU) and usefulness (NU > NS). c, f) The mean percent signal changes separately for the left MTL (include left HIP and left PHG) and d, e) right MTL (include right HIP and right PHG) across the 3 experimental conditions in 6 s, 8 s, and 10 s. error bars represent the SEM. Asterisks indicate significant differences between conditions ($^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.001$). FU, familiar useful; NS, novel useless; NU, novel useful.

the novel stimulus with high usefulness (NU stimulus; signal change NU>NS/FU).

Distinct AIs in the MTLs during novelty and usefulness processing

We calculated the AIs of the MTL regions during novelty and usefulness processing with the formula: $AI = L - R/|L| + |R|$. The result showed that the right MTL is predominant in novelty processing (NU-FU: $t_{HIP}(18) = -0.47$, $P = 0.646$, $t_{PHG}(18) = -2.09$, $P = 0.05$, P value are 2-tailed). However, the left MTL is predominant in usefulness processing (NU-NS: $t_{HIP}(18) = 2.55$, $P = 0.02$, $t_{PHG}(18) = 2.35$, $P = 0.03$, P value are 2-tailed) (Fig. 3). This result suggests that the usefulness processing is functionally lateralized in the left MTL, while the novelty processing is functionally lateralized in the right MTL.

Distinct functional pathways in 2 hemispheres PHG to identify NS and NU stimuli

Next, we conducted a PPI analysis to identify the functional coupling of bilateral PHG separately with every other voxel of the brain.

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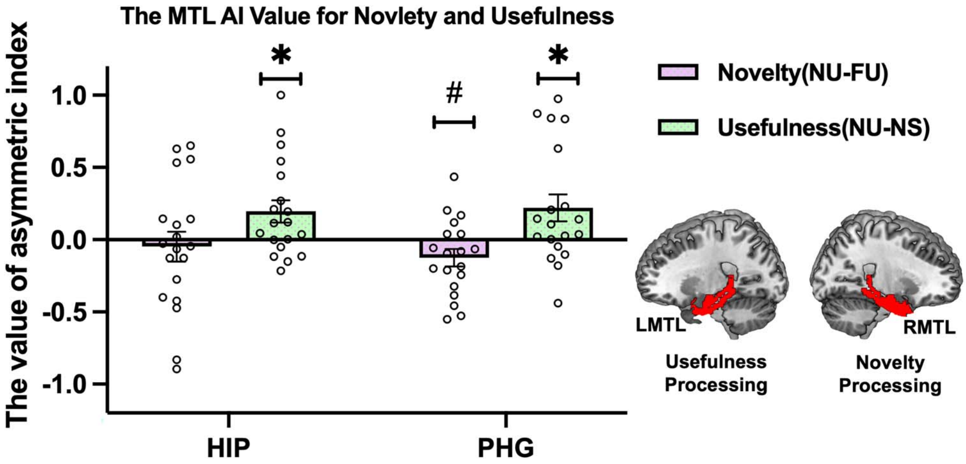

Fig. 3. Distinct novelty and usefulness processing in the left and right MTL. The AI of the right MTL is significantly greater than that of the left MTL in novelty processing (NU-FU); whereas the AI of the left MTL is significantly greater than that of the right MTL in usefulness processing (NU-NS). The brain image displays the distinct novelty and usefulness processing in left and right MTL (red). Error bars represent the SEM. Asterisks indicate significant differences between conditions (*$P < 0.05$, **$P < 0.01$, #$P = 0.05$). FU, familiar useful; NS, novel useless; NU, novel useful.

For left PHG, the result revealed significantly higher left PHG functional coupling with brain regions of the right HIP in the processing of NU condition compared with NS condition. Significantly higher left PHG functional coupling with brain regions of inhibitory control (right superior frontal gyrus and left medial frontal gyrus) were observed in the processing of NS condition compared with NU condition. For the right PHG, the result revealed no significant increases in coupling in the processing of the NU condition compared with the NS condition. In comparison, significantly higher right PHG functional coupling with several brain regions, including the amygdala, midbrain, PHG, superior occipital/temporal gyrus, and several frontal regions, were observed in NS condition compared with NU condition (Supplementary Table S2).

Moreover, we performed a SVC in the PPI result with the cluster-level FWE correction for the ACC, amygdala, midbrain, and HIP. The result showed that the ACC region has significant functional connectivity with both left and right PHG, but a small cluster size of ACC shows functional connectivity with right PHG. The right PHG has significant functional connectivity with the amygdala, midbrain, and HIP (Supplementary Table S3).

Finally, we extracted the functional connectivity between left/right PHG and ACC. The result showed that the functional connectivity between left PHG and ACC was significantly stronger than between the right PHG and ACC (Fig. 4A). Next, we computed the functional connectivity between right PHG and amygdala, midbrain, and HIP, to compare the functional connectivity strength between NS and NU processing. The result showed that the functional connectivity strength during NS processing was significantly higher than during NU processing (Fig. 4B). The result indicates that the left PHG has stronger functional connectivity with the executive control system (ACC). In comparison, the right PHG has stronger functional connectivity with the emotion system (amygdala), the reward system (midbrain), and the memory system (HIP) in the NS condition than in the NU condition.

Distinct multivoxel representational patterns in left and right MTL

We conducted a similarity analysis to find the neural pattern representation differences between the left and right MTL regions. First, we compared the neural pattern dissimilarity difference between the left and right MTL across the 3 conditions (between FU and NS, FU and NU, NS and NU) to investigate the difference between the left and right MTL in neural distinction among the 3 conditions in the inter-condition analysis. The dissimilarity between FU and NU represents the ability of the left/right MTL to discriminate novelty information between these items. Similarly, the dissimilarity between NS and NU represents the ability of the left/right MTL to discriminate usefulness information between these items. Second, we computed the neural pattern dissimilarity between left and right MTL within the 3 conditions (within FU, NS, and NU) to investigate the difference between left and right MTL in neural distinction within each condition in the intra-condition analysis. The items in the same condition still have subtle differences in novelty and usefulness. Here, we investigate the discrimination between the left and right MTLs for different items within the same condition.

For the PHG, the dissimilarities for all conditions (FU vs. NS: ($t(18) = 2.20$, $P = 0.041$, $d = 0.504$), FU vs. NU: ($t(18) = 2.43$, $P = 0.026$, $d = 0.558$), NS vs. NU: ($t(18) = 3.41$, $P = 0.003$, $d = 0.783$)) showed were significantly higher on the left than right. For HIP, the result showed that only the dissimilarity between NS and NU were significantly higher in the left than right side ($t(18) = 2.61$, $P = 0.018$, $d_{as} = 0.599$), but not between FU and NU ($t(18) = 1.65$, $P = 0.116$, $d = 0.379$) or between FU and NS ($t(18) = 1.35$, $P = 0.195$, $d = 0.309$) (Fig. 5A; a1, a2).

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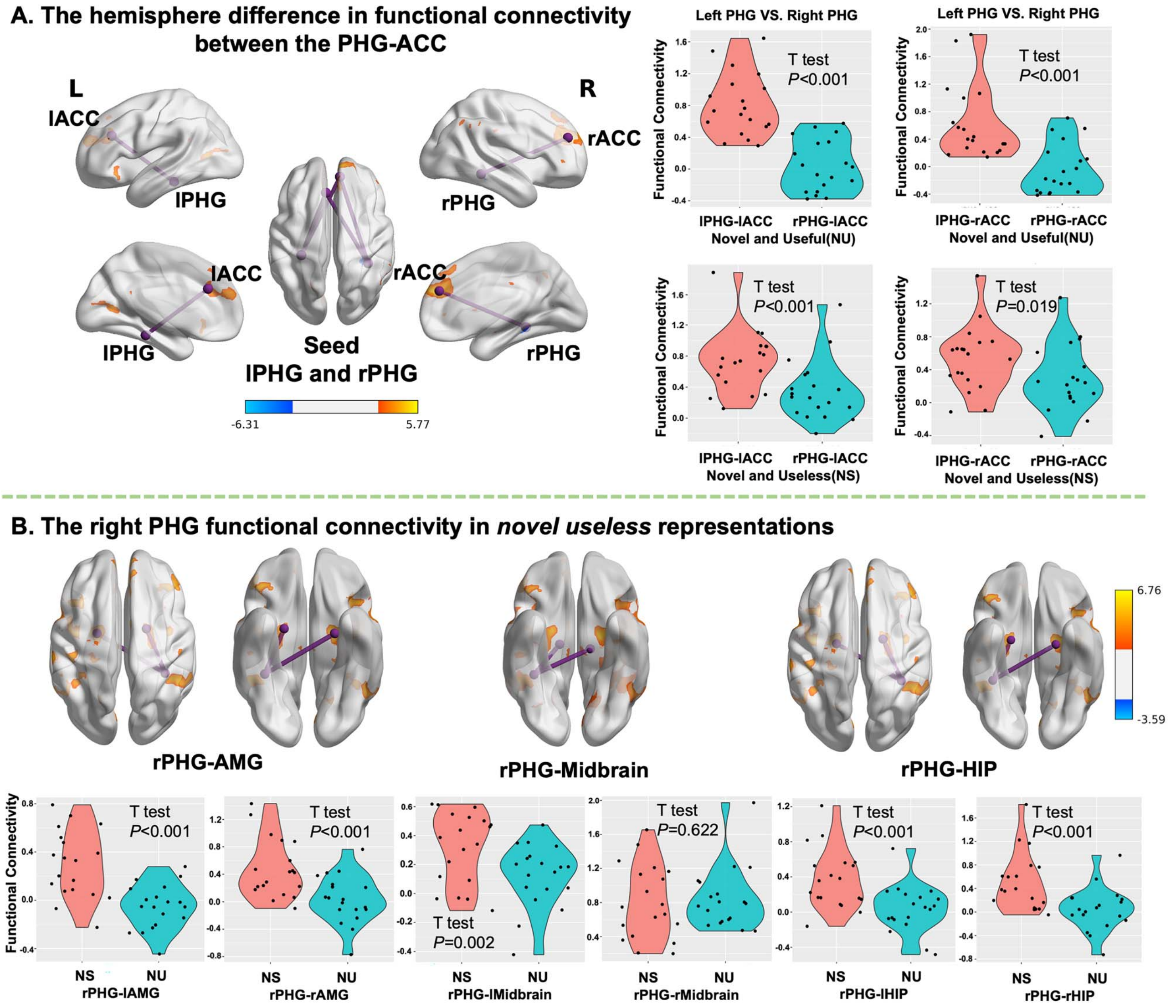

Fig. 4. Distinct functional pathways to NS stimulus representations between the left and right PHG. A) The hemisphere difference in functional connectivity between the PHG and ACC. The brain image shows the functional connectivity between seed region of bilateral parahippocampal (MNI, left PHG peak x = −30, y = −32, z = −18, right PHG peak x = 36, y = −40, z = 10) and ACC, the activation regions showing positive (red) and negative (blue) associations with left and right PHG activation modulated by the novel useless object relative to a novel useful condition (NS vs. NU). Violin graphs represent the functional activation in the ACC showing higher engagement in the functional connectivity of left PHG–ACC than the right PHG–ACC. B) The right PHG functional connectivity in NS representations. The brain images represent the functional connectivity activation in the AMG, midbrain, and HIP. Violin graphs showing the functional connectivity of right PHG–AMG, right PHG–midbrain, and right PHG–HIP with higher engagement in the novel and useless condition relative to the novel and useful condition (NS vs. NU). The color bar represents T values. AMG, amygdala; L, left; R, right; MNI, Montreal neurological institute coordinate system.

For the PHG, the result showed that the dissimilarity within FU was significantly higher in the left side than the right side ($t(18) = 3.47$, $P = 0.003$, $d = 0.796$), and the dissimilarity within NS ($t(18) = 3.59$, $P = 0.002$, $d = 0.823$) and the dissimilarity within NU ($t(18) = 2.55$, $P = 0.02$, $d = 0.585$) display the same pattern. But for HIP, the result showed that the dissimilarity within FU ($t(18) = 1.17$, $P = 0.256$, $d = 0.269$), the dissimilarity within NS ($t(18) = 1.87$, $P = 0.078$, $d = 0.429$), and the dissimilarity within NU ($t(18) = 1.21$, $P = 0.242$, $d = 0.277$) were no significant differences between left and right side (Fig. 5A; a3, a2).

The result showed that the left MTL representation pattern is stronger than the right MTL in distinguishing the novelty and usefulness differences in inter-condition (across the 3 conditions) and intra-condition (within each condition).

The left PHG pattern similarity predicts behavior score

Further analyses revealed that higher multivoxel pattern similarity in the left PHG was positively predictive of higher usefulness score ($r_{(\text{predicted, observed})} = 0.48$, $P = 0.021$) and creativity score (novelty plus usefulness) ($r_{(\text{predicted, observed})} = 0.44$, $P = 0.037$) in NU designs (truly creative product), but not the right PHG ($P_{(\text{usefulness})} = 0.64$; $P_{(\text{creativity})} = 0.59$) (Fig. 5B). The result indicates that the

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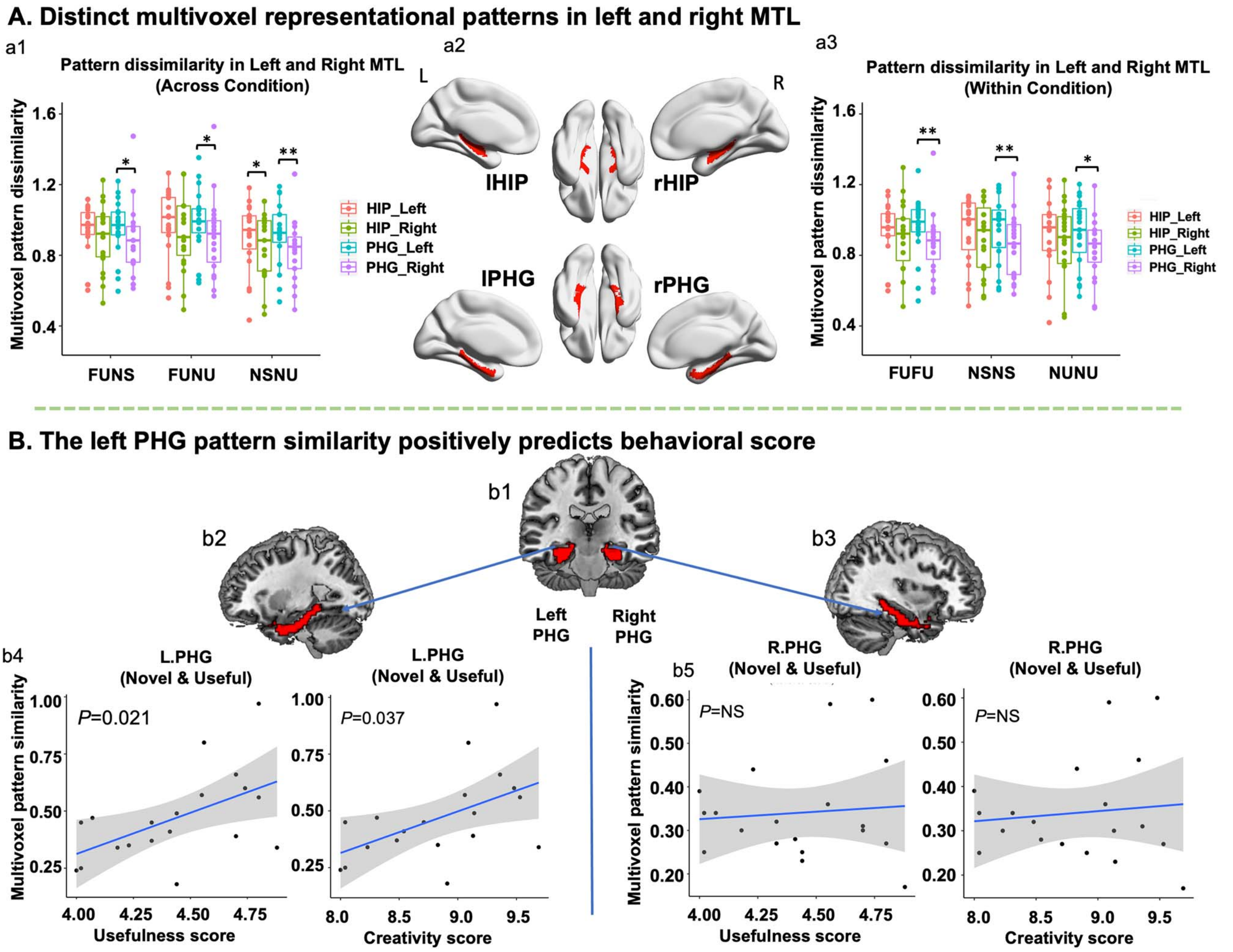

Fig. 5. A) Distinct multivoxel representational patterns in left and right MTL. a1, a3) The multivoxel representational patterns dissimilarity difference between the left MTL and right MTL across (a1) or within (a3) the 3 conditions. a2) The structural ROIs of the left and right MTL used in the representational pattern similarity analysis. B) The left PHG pattern similarity positively predicts behavioral score. b1, b2, b3) The structural ROIs of the left and right PHG (seed). b4) The higher multivoxel pattern similarity in the left parahippocampal was positively predictive of higher usefulness scores ($r_{(\text{predicted, observed})} = 0.48$, $P = 0.021$) and creativity scores (novelty plus usefulness) ($r_{(\text{predicted, observed})} = 0.44$, $P = 0.037$) in NU design (truly creative product), and b5) with no significant results in right parahippocampal ($P_{(\text{usefulness})} = 0.64$; $P_{(\text{creativity})} = 0.59$). Asterisks indicate significant differences between conditions (*$P < 0.05$, **$P < 0.01$). L, left; R, right. NU, novel useful; NS, novel useless.

left PHG pattern similarity is positively associated with behavioral usefulness and creative evaluation.

Discussion

We demonstrated the lateralization of the left and right MTL during creative novelty and usefulness evaluation. Results revealed that the right MTL is predominantly implicated in the "novelty" processing of creative thinking, with the criterion of response to novel stimuli being lenient, showing strong functional connectivity with the limbic system (amygdala), reward regions (midbrain), and the episodic memory system (HIP). In contrast, the left MTL is predominantly involved in the "usefulness" processing in creative thinking, with the criterion of response to novel stimuli being stringent, showing strong functional connectivity with the executive control system (ACC). Moreover, the multivoxel representational patterns showed that the left MTL representation pattern is more effective than the right MTL in distinguishing the usefulness features in novel stimuli, successfully predicting behavioral "usefulness" and "creativity" scores of "truly creative" products. Together, these findings provide novel evidence for the differences between left and right MTL during processing regulated by novelty and usefulness.

First, our findings showed a different signal activation pattern across time between the left and right MTL regions, and AIs showed that right MTL was predominantly involved in novelty processing. Our results are consistent with the model of "coarse versus fine" semantic coding in the right and left hemispheres (Beeman et al. 1994, 2000; Beeman and Bowden 2000; Beeman and Chiarello 2013). This model suggests that the right hemisphere is mainly involved in coarse semantic coding, including secondary word meanings, or information that is only remotely related to the input word (Chiarello et al. 1992; Chiarello and Richards 1992;

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Beeman et al. 1994, 2000; Bowden and Beeman 1998; Beeman and Bowden 2000; Bowden and Jung-Beeman 2003; Beeman and Chiarello 2013). Furthermore, previous studies have demonstrated that the right hemisphere is predominantly involved in facilitating novel and original ideas or coming up with open-ended problems, especially for metaphoric or connotative meaning (Spring and Deutsch 1981; Mashal et al. 2005; Mashal and Faust 2008; Marinkovic et al. 2011; Beaty and Silvia 2013; Beeman and Chiarello 2013), artistic action (Kowatari et al. 2009), as well as visuospatial-related creativity (Chen et al. 2019). EEG studies, meanwhile, have suggested that artists show greater synchrony within the right hemisphere than the left hemisphere (Bhattacharya and Petsche 2002). Creativity often refers to generating novel or unusual associations (Moscovitch et al. 2016; Luft et al. 2018; Cabeza et al. 2020; Thakral et al. 2020). Multiple studies reveal that the HIP and its connected regions are essential for novel associations (Luo and Niki 2003; Cabeza et al. 2020; Thakral et al. 2020). In conjunction with our result, it is not surprising that right MTL dominated in novelty processing and involves the novel information process in both "useful" and "useless" novel designs—suggesting that right MTL plays a role in broadly novel associations, irrespective of usefulness.

Second, we found that the left MTL was predominantly involved in usefulness processing and only responded to NU designs. Through prior studies, it is well established that the left hemisphere is central for verbal and semantic language functions (Tzourio-Mazoyer et al. 2004; Greve et al. 2013; Wang et al. 2019) and executive control (MacDonald et al. 2000; Wood and Grafman 2003). Here, the left MTL's function may have been affected by those same lateralized functions. On the one hand, previous studies demonstrated that creative processes have a critical role in forming new concepts in the HIP and middle temporal gyrus (MTG), especially for meaningful novel concept formation in the left side of the MTG (Ren, Huang, et al. 2020a). Moreover, the "fine semantic coding model in the left hemisphere" suggests that the left hemisphere strongly activates smaller areas of semantic information closely related to words in the context (Beeman et al. 1994; Beeman and Bowden 2000; Beeman et al. 2000; Beeman and Chiarello 2013), which implies that the remote-related semantic information is hard to associate each other, while it is critical to forming the novel association. It causes a strong association from prior knowledge activates as highlight semantic information, hindering the remote-related semantic association, such as the secondary or implicit semantic information. In conjunction with our results, even the NS designs potentially have some value (e.g. the "deadwood cracks" desk could be used as a work of art), it is hard to detach the strong semantic association of "desk-office" to form the secondary meaning or implicit novel association of "desk-sculpture." This causes the left hemispheres' semantic system to have stronger activation in highlighting semantic information than remotely related ones. Our previous study also proved that detaching oneself from an object's original use is not easy. Once objects are made 'useless' by removing their original functionality, it requires more effort to see these useless objects as valuable, not only functionally but also creatively (Ren, Huang, et al. 2020a).

On the other hand, the executive control mechanisms lateralized in the left hemisphere (Tzourio-Mazoyer et al. 2004; Greve et al. 2013; Wang et al. 2019) could affect novel association processing in the left MTL. Previous studies showed that dorsal ACC and the frontal regions are critical hubs in a domain-general executive function network (Shenhav et al. 2016), essential for error detection (Ito et al. 2003; Narayanan et al. 2013; Shen et al. 2015), explicit negative feedback (Quilodran et al. 2008), and conflict (Sheth et al. 2012; Oehrn et al. 2014; Michelet et al. 2016; Tang et al. 2016), as well as critical roles in the late task control signal (Neta et al. 2017). Previous studies have suggested that executive control mechanisms show high activation when humans encounter a new or unfamiliar stimulus—since unfamiliar stimuli in nature are frequently associated with danger (Tiitinen et al. 1994; Boddez et al. 2013). One explanation would be that the NS stimulus can result in activation within the executive control systems, which in turn leads to the left MTL combined with executive control systems taking a role of screening and evaluating the usefulness in novel association processing (Seeley et al. 2008; Mayseless et al. 2014). Our finding suggests that the executive control mechanism predominant in the left hemisphere affects novel associations. This is consistent with the idea that decreased inhibition from the left hemisphere can facilitate the emergence of creativity (Seeley et al. 2008; Huang et al. 2013; Mayseless and Shamay-Tsoory 2015; Rémi et al. 2015). Moreover, as the current study focuses on the creativity evaluation, the executive control mechanism may also act as a screening process to decide whether to accept the displayed novel associations. This is consistent with the previous studies, showing stronger activation in a left-lateralized neural network (e.g. superior frontal brain) when exposed to other people's ideas (Fink et al. 2010, 2012; Huang et al. 2018). Furthermore, our findings also align with prior data implicating functional connectivity between the DMN (including MTL) and the executive control system, suggesting that the 2 systems tend to cooperate during creative cognition despite their possible antagonistic relations (Ellamil et al. 2012; Liu et al. 2015; Beaty et al. 2016). Taken together, the left MTL collaborates with the executive control system to evaluate and screen the useless novel associations, and the DMN and executive control system may cooperate during creative evaluation.

By contrast, we observed functional connectivity between right PHG and bilateral amygdala, bilateral midbrain, and bilateral HIP. Coordinated functional interactions between right PHG and amygdala were shown in the right hemisphere's novel association processing, implying emotional activation during the novel

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association processing. Indeed, clinical observations have suggested a predominance of the right hemisphere for all kinds of emotions (Craig 2005; Gainotti 2012, 2019). The amygdala is known to play a critical role in emotional arousal (McGaugh 2004; Phelps and LeDoux 2005), and the activation level of the amygdala reflects the intensity of emotional arousal for both positive and negative emotions (Löw et al. 2008; Shabel and Janak 2009; Costa et al. 2010; Fastenrath et al. 2014). The amygdala is known to show hemispheric asymmetries, with the right amygdala mainly activated in stimuli processed below the level of awareness (Morris et al. 1998; Gainotti 2012), rapid detection of emotional stimuli (Gläscher and Adolphs 2003; Wright et al. 2003), and predominance for all kinds of emotions (Gainotti 2019). In contrast, the left amygdala is preferentially activated by consciously processed emotional stimuli (Morris et al. 1998; Williams et al. 2006) and plays a critical role in evaluating more elaborate stimuli (Gläscher and Adolphs 2003; Wright et al. 2003). Moreover, previous magnetoencephalography (MEG) studies showed that the amygdala processes threat-related information through a fast right subcortical route and a slower left cortical feedback mechanism (Hung et al. 2010). Here, our result of the functional connectivity between the right PHG and bilateral amygdala indicates that the right hemisphere's novel association processing possibly involves emotional processing.

We also observed connectivity between the right PHG and the midbrain and HIP. The previous studies suggested that the midbrain is a region critical to reward-related processing (Adcock et al. 2006; Wolosin et al. 2012) and curiosity-driven reward learning (Gruber et al. 2014) and the HIP is the main region involved in episodic memory (Eichenbaum et al. 2007; Wixted and Squire 2011; van Kesteren et al. 2012; Palombo et al. 2015; Moscovitch et al. 2016) and related to reward experience (Wittmann et al. 2007; Krebs et al. 2009, 2011; Bunzeck et al. 2010, 2012). Our result here revealed that the novel stimulus might promote a reward experience through the HIP-dependent dopamine circuit. Additionally, we found that the right PHG has functional connections to visual areas such as the middle occipital gyrus, temporal lobe, parietal lobe when responding to NS stimuli, which indicates that the right PHG may respond to the novel information more broadly (both useless and useful) from the perception (e.g. visual cortex). The functional connectivity between the right PHG and these regions indicates that novel associations can be positive salient experiences that activate emotional systems through the HIP-dependent dopamine circuit.

Furthermore, results from multivoxel pattern similarity revealed that left MTL had a stronger representation in distinguishing novel stimuli than right MTL. Accordingly, MTL regions—such as the HIP and PHG—are particularly crucial for response to the novel information, including novel stimulus detection (Blackford et al. 2010; Kafkas and Montaldi 2014), recombination of stored novel episodic and semantic information (Wixted and Squire 2011; Madore et al. 2016; Beaty et al. 2018, 2020), and new concept learning (Schapiro et al. 2012; Mack et al. 2016) as well as forming useful novel associations (Luo and Niki 2003; Hassabis and Maguire 2007; Duff et al. 2013; Backus et al. 2016) and new usefulness concepts (Ren, Huang, et al. 2020a). The larger pattern representational dissimilarity between NU and NS designs in left MTL possibly indicated that the neural-based functional distinction in processing usefulness features is stronger in the left than right MTL. Consistent with our finding, many previous studies suggested that the left HIP predominated in the meaningful (as opposed to nonsense) semantic concept-related association (Strange et al. 1999; Ezzati et al. 2016). In addition, our result showed that the left PHG neural pattern similarity robustly predicted usefulness and creativity scoring in NU designs. It confirmed that left MTL has a particular neural representation pattern and affects behavioral usefulness evaluation in genuinely creative designs.

We expand the two-fold model of creativity, proposing a left–right hemispheric mechanism model for creativity (Fig. 6). This model describes functional differences in the processing of creative novelty and usefulness between the left and right brains during creative design evaluation. It includes three processing phases involved in four major cognitive systems: the novel association system, the semantic concept system, the executive control system, and the emotional reward system.

The four cognitive systems involved in the left–right hemispheric mechanism model for creative evaluation

a. Novel association system, mainly related to the HIP adjacent to the MTL. Creativity involves the formation of "novel associations" and "creative conceptualization" (Ren, Huang, et al. 2020a; Zhang et al. 2020). The "novel associations" system predominantly involves the formation of novelty representation—it associates/reorganizes the novel information and integrates/represents the concept information by the HIP and semantics/association. Although the novel association involves the concepts/semantics association processing system, it predominantly involves semantic concepts association rather than creative conceptualization. Additionally, our previous publication (Ren, Huang, et al. 2020a) showed that novel association is not necessarily associated with creative conception, as, for example, is the case with NS designs. Subjects prefer to classify NS and FU as the same category, suggesting that novel associations may not lead to creative conceptualization, whereas the NU designs belongs to a different category (Ren, Huang, et al. 2020a). The MTL has lateralization for processing novel stimuli between left and right sides: the left MTL is stringent with new stimuli processing and predominates in the usefulness processing, while the right MTL is more lenient and predominates in novelty processing. This processing preference is determined by the difference in left and right MTL's pattern representation during new stimuli

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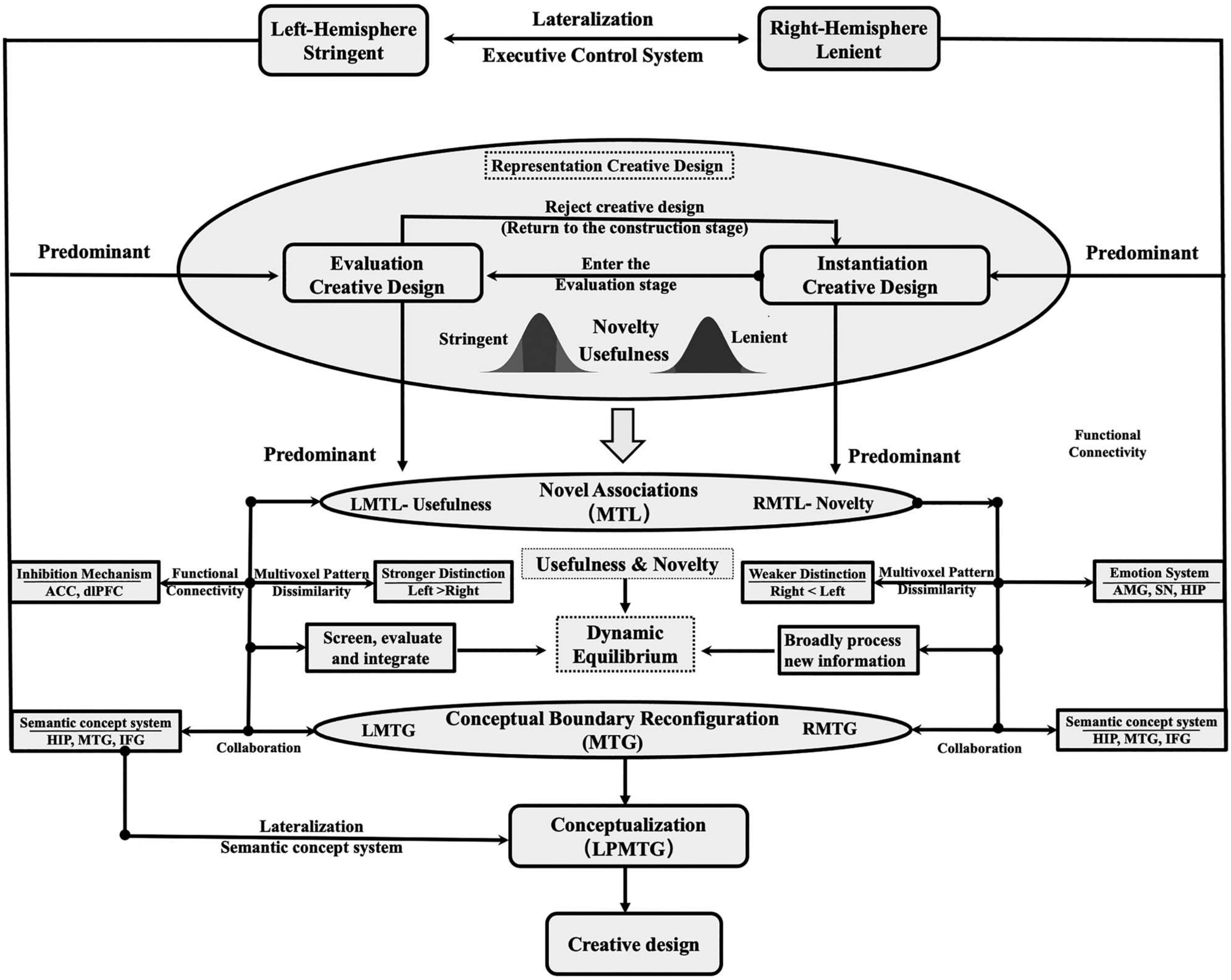

Fig. 6. The left–right hemispheric mechanism for creative evaluation. This model describes functional differences in the processing of creative novelty and usefulness between the left and right brains during creative design evaluation. It includes three processing phases involved in four major neural-based cognitive systems: the novel association system, semantic concept system, executive control system, and emotional reward system. HIP, hippocampus; PHG, parahippocampal gyrus; LPMTG, left posterior middle temporal gyrus; ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; AMG, amygdala; SN, substantia nigra; L, left; R, right.

and the interaction with the lateralization of semantic concept system, executive control system, and emotional reward system.

b. Semantic concept system, critical for the semantic concept process. It involves the extraction, representation, association, and integration of semantic concept information in creativity generation and evaluation. It is also crucial for concept reconfiguration to break the previous concept boundary and form the creative concept. The creative concept needs successfully integrate the semantic concept information and reconfiguration concept boundary based on the formed novel associations. This process mainly relates to the posterior MTG, especially the left posterior MTG (Shen et al. 2017; Ren, Huang, et al. 2020a), and cooperating the brain regions of the HIP, inferior frontal gyrus (IFG), and mainly lateralized in the left hemisphere. Creativity relies on the reorganization of existing knowledge to generate novel and useful concepts. Although novelty and usefulness processing play a critical role in new concept and category formation in creativity, the usefulness processing tends to acquire the meaningful semantic in the concept process, which lateralizes in the left hemisphere. Therefore, stringent/lenient evaluation semantic concept criteria predominate in the left hemisphere have a more significant influence on creative usefulness than novelty process.

c. Executive control system, including the anterior cingulate gyrus (ACC) and the dorsolateral prefrontal cortex, mainly lateralized in the left hemisphere. The left and right hemispheric mechanisms depend on the left-lateralized executive control system. All the evaluation creativity processes are affected by the executive control system. Our studies suggest that functional connectivity between the left MTL and executive control system during the creative evaluation process implies that the left MTL predominates usefulness processing to screen, evaluate, and integrate novel association information.

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d. Emotional reward system, including the amygdala, HIP, and midbrain. Functional connectivity between the right MTL and the emotional reward system during the creative evaluation process implies that the right MTL predominates novelty processing, with the low acceptance criterion to process broadly novel associations for novelty and usefulness integration. Together, these four cognitive systems lead to the lateralization of creative processing between the left and right hemispheres. Through the interaction of these cognitive systems, the novelty and usefulness evaluation criterion between the left and right hemispheres may reach a dynamic balance.

The three processing phases in the left–right hemispheric mechanism model for creative evaluation

a. Representation of the creative design—forming a representation of the design comprises of the "instantiation" and "evaluation" substages. In the context of this experiment, the "instantiation" stage was externally induced (through the presented creative designs) to instantiate the designs in one's imagination. Here, the "instantiation" substage shares some functional description with the "generation" stage in the "two-fold model of creativity," both of which relate to the production of "creative generation." However, since the current model is predominantly about creative design evaluation—the "instantiation" subprocess in this context functions specifically to produce a subjective form of visual representation within conscious awareness. The "evaluation" substage is thus aimed at evaluating the instantiated image, which is assessed for "novelty" and "usefulness." This evaluation process is dynamic—from "lenient" to "stringent"—depending on the environment, individual differences, and hemispheric lateralization. Too "stringent" evaluation leads to excessive rejection of creative ideas, while too "lenient" evaluation leads to increased acceptance of low-quality creative ideas. Within this model, left–right hemisphere lateralization is involved in the evaluation process based on "novelty" and "usefulness," with the left hemisphere is primarily responsible for a "stringent" evaluation, and the right hemisphere is predominantly responsible for a "lenient" evaluation. There are several caveats for the representation phase. Firstly, there is a general interdependence and recursive processing between "instantiation" and "evaluation" substages: these are not necessarily conducted in a linear sequence but simultaneously and dynamically. Secondly, there is functional lateralization between the left and right hemispheres: The right hemisphere predominates the instantiation substage, while the left hemisphere predominates in the evaluation substage. Thirdly, the evaluation substage is not solely involved in the "representation" stage but is also employed in the "novel association" and "conceptual boundary reconfiguration" stages in conjunction with other cognitive systems. Moreover, the evaluation in the representation stage is only related to evaluating the instantiation creative design, not the final design decision, rejection, and acceptance.

b. Novel association phase—the attribution of novel associations, based on the evaluation criterion of "novelty" and "usefulness." The left and right MTL have different roles in novelty and usefulness processing. The right MTL is predominantly involved in the novelty processing, with weaker usefulness pattern distinction. It has functional connectivity with the emotion system to process the novel information broadly. The left MTL is predominantly involved in the usefulness processing, with stronger usefulness pattern distinction, and has functional connectivity with the executive control network (ECN) to screen, evaluate, and integrate the novelty and usefulness. In this step, both the left and right hemispheres process novelty and usefulness. Still, there are different processing priorities for novelty or usefulness depending on the left or right hemisphere. A novel association is evaluated when the right and left hemispheres coordinate their participation in novelty and usefulness processing.

c. Conceptual boundary reconfiguration—the process of reconfiguring the conceptual boundary of the novel design to include the novel associations conceptualized within the creative design. During this process, the conceptual boundary of the creative design is dynamically adjusted in proportion to the evaluated "novelty" and "usefulness" until a creative conceptualization is completed. After the creative conceptualization, the conceptual boundary for the specific design is fixed. Therefore, only the genuinely novel designs—that "break" the familiar conceptual boundaries—can be considered real "creative" design. Through this process, the conceptual boundary around the "familiar design" is never changed, as it is only a reference point against which to evaluate creative content. For the novel design (NS, NU), the conceptual boundary dynamically changes as it functions beyond the boundaries of the previous concept. However, the NS design fails the creative conceptualization, as the usefulness is not sufficient to break the original conceptual boundary. On the contrary, the NU design successfully breaks this conceptual boundary. This process involves the left posterior MTG in cooperation with the semantic concept system (Ren, Huang, et al. 2020a).

The relationship between the two-fold model and left–right hemispheric model in creativity

The definition of generation

Compared with the "two-fold model" of creativity (Ellamil et al. 2012; Mayseless et al. 2014; Kleinmintz et al. 2019), the term "generation" in the left–right hemispheric model of creativity is defined as "instantiation"—it is distinct from the ideas generated in divergent thinking, which is induced by the creative designs, leading to the generation of a representative image by induced creative design. Although the instantiation process is guided by externally induced information, there is a specific component of self-construction based on creative design. Therefore, generation in the left–right hemispheric model of creativity is equivalent to the construction of an induced image,

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which comprises one part of a broader process that forms representations of the creative design.

The definition of evaluation

Beyond the two-fold model of creativity, evaluation throughout the whole three processing phases has a different aim in evaluation among the three stages in the left–right hemispheric model of creativity. The evaluation in the representation creative design phase aims to evaluate the construct design based on "novelty" and "usefulness," interacting to cooperate within the "instantiation" stage to form the representation of the creative design. Moreover, it only forms the essential representation to an understanding of the creative design, not the final decision of the design. The "evaluation" component in the novel association stage evaluates the novel association based on the "novelty" and "usefulness." There is interaction predominantly for left and right hemispheres in the novel association phase. Similarly, the evaluation in conceptual boundary reconfiguration aims to evaluate the conceptual boundary of the novel association based on novelty and usefulness. Therefore, the evaluation in the left–right hemispheric model of creativity is related to the whole creativity evaluation stage processing and plays different roles among these stages.

The extending of the two-fold model of creativity

The left–right hemispheric model is beneficial for understanding the difference between the left and right hemispheres in creativity evaluation and lateralization between left and right MTL in "novelty" and "usefulness" processing. It is a valuable extension and supplement to the two-fold model of creativity.

Limitations

There are several limitations to this study. Firstly, the sample size of this study is not large. Although the number of subjects in the current research aligns with our group's previous studies (Huang et al. 2015, 2018), it may have been limited to detect smaller effects. However, the previous study investigated sample size in event-related fMRI study showed that although the power was inferior in the range of most conventional fMRI studies (10–20 subjects), most activated areas were true positives (Murphy and Garavan 2004). We hope future studies will include larger fMRI-scanned samples. Second, in the current study, we focused on the evaluation process of creativity, but not the generation process. The left–right hemisphere lateralization of the generation process still needs to be examined. Third, we hypothesized that the left–right creativity evaluation mechanism is focused on the brain regions of MTL. Although the MTL has been shown to be involved in the novel association (Luo and Niki 2003; Wixted and Squire 2011; Palombo et al. 2015; Cabeza et al. 2020; Zhang et al. 2020; Ren, Huang, et al. 2020a), other regions (e.g. MTG) are also involved (Ren, Huang, et al. 2020a). Further study could broaden the MTL regions to the whole brain to study the left–right creativity evaluation mechanism.

Conclusion

Our study used fMRI to demonstrate the functional lateralization within specific brain structures of MTL in associative processing regulated by novelty and usefulness evaluation. Our findings indicate that right MTL predominates novelty processing, broadly processing new information and forming new associations. The left MTL predominates usefulness processing to screen, evaluate, and integrate novelty and usefulness information and combines both left and right MTL to represent the NU association. The current results thus provide novel insights into a longstanding and controversial question in creativity research by demonstrating that the distinct functional lateralization in the process of novel association for the mechanism of a left–right hemispheric MTL supports the two hemispheric functional differences and interaction in creativity evaluation.

Supplementary material

Supplementary material is available at *Cerebral Cortex Journal* online.

Authorship contributions

JR and JL conceived and designed the experiment. JR made the experiment materials, conducted the fMRI and behavioral experiment, performed data analysis, made the figures, and wrote the original manuscript. JR, JL, SQ, and MD advised on results interpretation and supported funding acquisition. All authors commented and edited the manuscript.

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