Classification: biological sciences, neuroscience

Reproducible observations revealing patterns of the default mode network underlie rumination

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ABSTRACT

Rumination is a specific form of self-generated thoughts and posited to be the psychological expression of abnormalities in the default mode network (DMN) in patients with major depressive disorder (MDD). Although converging lines of evidence link the neural basis of MDD and the DMN, the mechanisms through which DMN regions cooperatively underlie rumination remain largely unclear. Here, with a modified continuous state-like paradigm, we induce healthy participants to ruminate or imagine objective scenarios (as a distraction control condition) on 3 different MRI scanners. We compared functional connectivities (FC) and inter-subject correlations (ISC) of the DMN and its 3 functionally-defined subsystems between rumination and distraction states. Results yielded a highly reproducible and dissociated pattern. During rumination, within-DMN FC was generally decreased compared to the distraction state. At the subsystem level, we found increased FC between the core and medial temporal lobe (MTL) subsystem and decreased FC between the core and dorsal medial prefrontal cortex (DMPFC) subsystem and within the MTL subsystem. Furthermore, we found decreased ISC within the MTL subsystem. These results suggest that DMN regions interacted with each other differently and are activated less synchronously across subjects during rumination and shed new light on the association between rumination and MDD patients' DMN abnormalities.

KEYWORDS: functional MRI, major depressive disorder, self-generated thought

SIGNIFICANCE STATEMENT

Rumination is widely accepted as the psychological expression of default mode network (DMN) alterations in patients with major depressive disorder (MDD), but our understanding of the DMN's mechanistic involvement remains rudimentary. Here, with a repeated measure continuous paradigm, we systematically examined how DMN subsystems underlie rumination. We found distinct patterns of functional connectivity within subject and less synchronized neural activities across subjects in DMN during rumination. These findings can help illuminate the association between rumination and DMN alterations in MDD. Confidence in our hypothesis-driven results is enhanced by their high reproducibility across three different scanners.

Introduction

Rumination is generally defined as a recurrent and passive focus on depressed mood itself and its possible causes and consequences (1). As a specific form of self-generated thoughts, rumination is common when people are expressing distress and is characterized by self-focused, past-oriented, negative thinking forms, highly automatic dynamic phenomenology, and contents of thought restricted to narrow themes (2, 3). Studies have implicated its pivotal role in the onset, maintenance as well as phenomenology of major depressive disorder (MDD) (4). Moreover, rumination is also deemed as the psychological expression of MDD patients' alterations within the default mode network (DMN) (5). Indeed, convergent lines of evidence suggest the DMN may be the key brain network supporting rumination (6). Using typical task-based designs, researchers found DMN region activities were higher in rumination compared to distraction, which is a control condition requiring participants to focus on externally oriented thoughts that are unrelated to themselves (7-11). Another line of studies (12-15) revealed that the strength of functional connectivity (FC) within the DMN is associated with subjects' rumination traits in the resting state.

The DMN is a set of brain regions showing reduced activity during active attention demanding tasks (16-18). Systematic reviews and meta-analyses implicated the DMN in a number of different processes including remembering the past, scene construction and theory of mind (16, 19). These processes are posited to be forms of self-generated thought, with mental contents dependent on internally constructed rather than externally constructed representations (18, 20). Further evidence suggests these processes may correspond to 3 heterogeneous subsystems: the core DMN subsystem, the dorsal medial prefrontal cortex (DMPFC) subsystem and the medial temporal lobe (MTL) subsystem (21). In general, the core subsystem is proposed to be associated with self-referential processes and acts as the hub linking all three subsystems. The DMPFC subsystem mainly participates in theory of mind and mental simulations whereas the MTL subsystem plays an important role in autobiographical memory and generating novel thinking ensembles (21-23). These DMN brain regions are proposed to work collectively and adaptively to facilitate different forms of self-generated thoughts (16, 18). As a distinct form of self-generated thoughts, rumination has been proposed to be driven by specific interactions among subsystems of the DMN (20, 24). However, such proposals still lack direct empirical evidence.

Although resting-state fMRI studies have been utilized to study the rumination trait across participants (25), rumination task fMRI studies are more suitable to reveal DMN patterns during active rumination states. Due to its repetitive and self-perpetuating nature (26), rumination is particularly suitable for a continuous semi-task paradigm, in which participants are asked to maintain a certain kind of mental process for a relatively long period (27). Several studies have used this kind of paradigm to explore the network mechanisms of rumination. Berman et al. (28) induced MDD patients and healthy controls to memorize certain negative autobiographical events continuously for 6 minutes as a rumination induction. They compared FC between posterior cingulate cortex (PCC) and the rest of the whole brain in rumination and in typical resting state, and found enhanced FC strength during rumination compared to resting-state across MDD patients and healthy controls. In another study (29), MDD patients and healthy controls were induced either to ruminate or be distracted for 4.5 minutes after a negative autobiographical recall, but no FC difference between rumination and distraction was found. With support vector machine, Milazzo et al. (27) investigated the differences in FC strengths between rumination and other mental states and found FC involving amygdala best distinguished rumination. Intriguing but inconsistent, these studies have demonstrated the feasibility of the rumination state paradigm, but the heterogeneity in rumination induction strategies and control conditions suggests a more rigorous approach is required to investigate the DMN mechanisms underlying rumination.

Apart from FC, inter-subject correlations (ISC) have been found to be useful and reliable in detecting stimulus-driven responses within the DMN (30, 31). A recent study found ISC may also represent shared internal mental processes (32). Rumination is characterized by its specific phenomenological features: diverse in contents but shared in forms (2, 33), which could be reflected by ISC alterations. Another concern in the field is the lack of reproducibility of small sample size, hypothesis-driven fMRI studies (34, 35). Whereas practices such as data sharing, transparent study reporting and enlarging sample size also help (35), we addressed this issue straightforwardly by repetitively scanning all participants on 3 different scanners in counterbalanced order and report only reproducible results.

The present study sought to directly investigate the interaction pattern (FCs) and shared neural process (ISCs) within DMN when subjects are actively engaging in rumination. To do so, we 1) designed a modified continuous, self-driven rumination state task that can provide state-like data suitable for FC and ISC analysis; 2) delineated the DMN into 3 subsystems of core, DMPFC, MTL according to Andrews-Hanna and colleagues' studies (17, 23) and analyzed FCs and ISCs at the subsystem level; 3) assured reproducibility by scanning participants on three distinct scanners in counterbalanced order. We hypothesized that FC between core and MTL subsystems would be enhanced and ISCs within DMN subsystems would be altered during rumination.

We investigated rumination's DMN neural basis by conducting a modified rumination state task in a young healthy sample. After a baseline resting state scan, we prompted participants to recall several personalized negative autobiographical events as an affect induction. Then in 2 conditions, we used prompts to induce participants either to focus on themselves and think about the possible reasons as well as consequences of the events they just memorized (rumination) or imagine specific visually dependent images (distraction). These prompts were modified from the rumination induction task (36) and items from the Ruminative Response Scale (37), which were widely used in previous rumination studies. Prompts were displayed continuously on the screen and participants were told to maintain the psychological process until the prompts disappeared. Moreover, before the resting state and after all states, participants were asked to rate their subjective emotional level and reported the forms and contents of their thoughts after all states, so that we could validate our inductions (Figure S1). All participants underwent scans on 3 distinct scanners: a GE scanner (henceforth "IPCAS") at the Institute of Psychology, Chinese Academy of Sciences, a GE scanner (henceforth "PKUGE") and a Siemens scanner (henceforth "PKUSIEMENS"), both at Peking University (Figure S2). We compared the FCs and ISCs of DMN and its subsystems between rumination and distraction states and report only reproducible findings. More details are given in the SI text.

Results

Behavioral Results

Behavioral results revealed an extraordinarily reproducible pattern (Figure 1). Compared to distraction and resting states, the contents of rumination were more about past, self, others, in speech form, and made participants sadder ($p < 0.05$, Bonferroni corrected, Table S4). After negative autobiographical memory induction, participants' emotional ratings were significantly decreased (IPCAS: t = -6.32, p < 0.001; PKUGE: t = -7.71, p < 0.001; PKUSIEMENS: t = -6.28, p < 0.001) compared to baseline and remained decreased after rumination (IPCAS: t = -4.44, p < 0.001; PKUGE: t = -4.39, p < 0.001; PKUSIEMENS: t = -4.48, p < 0.001), but recovered to baseline or even higher than baseline after distraction (IPCAS: t = 2.76, p = 0.0088; PKUGE: t = 1.74, p = 0.09; PKUSIEMENS: t = 2.43, p = 0.02).

DMN Functional Connectivities

After the negative autobiographical memory induction, participants were either induced into rumination or distraction states. We first compared overall FC strengths within the DMN between rumination and distraction states. Results revealed overall decreased FC within the DMN during rumination as compared to distraction. This pattern was replicated on all 3 scanners (IPCAS: t = -2.27, p = 0.028; PKUGE: t = -2.25, p = 0.030; PKUSIEMENS: t = -3.33, p = 0.002, see Figure 2).

FCs Within and Between Subsystems of DMN

We further compared FCs within and between 3 subsystems of DMN in rumination and distraction states. Results revealed a reproducible but dissociate pattern. Specifically, FC between core and MTL subsystems was significantly enhanced in the rumination state as compared to distraction state (IPCAS: t = 1.30, p = 0.20; PKUGE: t = 2.36, p = 0.023; PKUSIEMENS: t = 2.88, p = 0.006). FC between core and DMPFC subsystem were significantly decreased in rumination state as compared to distraction state (IPCAS: t = -3.02, p = 0.004; PKUGE: t = -4.74, p < 0.001; PKUSIEMENS: t = -3.37, p = 0.002). FC within MTL subsystem in the rumination state was decreased versus the distraction state (IPCAS: t = -2.86, p = 0.007; PKUGE: t = -1.67, p = 0.101; PKUSIEMENS: t = -3.57, p = 0.001, see Figure 3A and 3B). Further analysis showed that the system level findings were also remarkably reproducible at the ROI level. Some intriguing alterations in FCs between ROI pairs were revealed. FCs among left MTL, left ventral posterior inferior parietal lobule (vpIPL) and right PCC as well as right rostral medial prefrontal cortex (RMPFC) were elevated in rumination compared to the distraction state. FCs between left DMPFC and several ROIs of the core subsystem and FC between left and right MTL were decreased during rumination as compared to distraction states (FDR corrected p < 0.05, Figure S3-4). We also analyzed the whole brain FCs of left and right MTL and results revealed that left MTL was functional connected to more brain regions and more strongly during rumination as compared to distraction state

(Figure S5).

ISCs within DMN

The comparison of ISCs within DMN revealed a decreased ISC within MTL subsystem in rumination as compared to distraction. This effect was significant on the PKUGE scanner ($t = -3.01$, $p = 0.005$) whereas a similar, albeit non-significant, pattern was detected on the others (IPCAS: $t = -1.55$, $p = 0.129$; PKUSIEMENS: $t = -1.41$, $p = 0.168$, see Figure 4A and 4B). Further ROI level analysis found that both hemispheres' retrosplenial cortexes (RSC)' ISCs were significantly decreased and other ROIs in the MTL subsystem showed a similar pattern except for the right MTL (Figure 4C and S6).

Discussion

Here we examined DMN FC and ISC patterns during rumination state with a continuous mental state paradigm. We found overall decreased FCs within DMN during rumination as compared to distraction state. Further DMN subsystem analysis revealed a more nuanced pattern: compared to distraction state, FC between the core and MTL subsystems was enhanced whereas FC between the core and the DMPFC subsystems as well as FC within the MTL subsystem was decreased. Furthermore, ISC within the MTL subsystem was also decreased. Of note, our results were robustly reproducible across 3 different scanners.

Participants' subjective reports revealed striking reproducibility across all 3 scanners. Emotional ratings showed that participants were in a dysphoric mood after recalling negative autobiographical events, indicating a successful negative affect induction. Because rumination is typically accompanied by psychological distress (4), we believe this induction functions as an effective facilitation. Furthermore, reported forms and contents of thinking were generally in line with rumination's phenomenological features: self-focused, negative and past oriented (4, 20, 33). To sum, behavioral self-ratings provided support for our paradigm in successfully inducing participants into a rumination state.

Our finding that FCs within DMN were decreased during rumination may seem counter-intuitive, but finer subsystem level analysis indicates this decrease may be driven by a dissociated FC pattern among different subsystems. Task based studies on rumination convergently found increased activity in the core subsystem as compared to distraction, but evidence regarding the other two subsystems has been less consistent (38). Previous rumination state studies indicated FCs between core subsystem region (PCC) and rest DMN regions may best differentiate rumination state and resting state (28). Resting state research mainly implicated scale-measured rumination trait with FCs of core subsystem region (RMPFC) (12, 13, 25). Whereas these previous studies provided informative regional evidence, our results provided an overall network-wise interaction pattern. Critically, our primary finding adds to the recent challenge to the prevailing notion that rumination causes the abnormally enhanced within DMN-FCs in MDD patients (39), indicating rumination's DMN neural underpinnings are more nuanced than previous hypothesis have predicted.

One particularly intriguing finding was the enhanced FC between the core subsystem and the MTL subsystem during rumination as compared to distraction state. This is in line with the notion that rumination may be caused by the too strong influence the core subsystem exerts on the MTL subsystem (20, 24). The core subsystem has been demonstrated to play an important role in processes such as self-referential perception, generation of affective meaning, and allowing individuals to construct and simulate alternative scenarios (21, 40). On the other hand, the MTL subsystem was proposed to engage in the retrieval of autobiographical memory and the generation of novel "blocks" of spontaneous thoughts (24, 41). Further ROI level analysis showed this effect was primarily driven by FCs among RMPFC, PCC and left MTL, which were all key regions underlying above-mentioned psychological processes (Figure S4). RMPFC and both MTLs were also demonstrated to be especially relevant to affect processes (3). Our results implicated that the over-constraint from core DMN regions (RMPFC and PCC) to the MTL subsystem regions (MTL) may lead to the key phenomenological features of rumination: repetitive, self-focus and negative valence (3, 20, 42).

We also found decreased FC between the core and DMPFC subsystems. The DMPFC subsystem was proposed to be linked to the theory of mind process, mental simulations and present-oriented thoughts (16, 23), but less involved in the generation of spontaneous thoughts, affective processes and past or future oriented thoughts (17, 20). Distraction is a present oriented, unrelated-to-self and non-affective mental state and has little to do with autobiographical processes (36). These features may lead to a stronger connection between the core and DMPFC subsystems during distraction as compared to rumination. Further ROI level analysis showed that the subsystem level difference was primarily driven by decreased FC between DMPFC and brain regions of the core subsystem. DMPFC projects less to the so-called “limbic system” and is associated with symbolic and universal rather than affective and motivational representations, which may be more involved in the distraction state (43, 44). Thus, it is possible that during rumination, brain regions of the DMPFC subsystem, especially DMPFC, cooperate less with the core subsystem because rumination consists of less symbolic, non-emotional and present oriented representations as compared to distraction. Together, these findings implicate the specific interaction modes among DMN subsystems that may characterize this very form of spontaneous thought: rumination.

We found that FCs within the MTL subsystem were decreased when participants were ruminating versus when they were distracted. This may be represented by the lateralization of both MTLs. Although they were both considered to be essential in autobiographical memory retrieving and generating spontaneous thoughts (24, 45), the left MTL was posited to be engaged in processing of verbal materials more than non-verbal materials (46, 47). Rumination is primarily in a verbal rather than imagery form, so left MTL may activate differently from right MTL during rumination, which probably reduces their FC. Indeed, our results showed left MTL was more widely and densely functionally connected to core DMN regions than right MTL during rumination as compared to distraction, indicating its more critical role in rumination (Figure S5).

Additionally, we found reduced ISCs within the MTL subsystem. Further ROI level analysis indicated an overall ISC decrease except for right MTL. Recent evidence revealed that similar DMN responses could also be observed when individuals were performing similar internal mental processes such as memory retrieval narrative understanding (32, 48). It is possible that similar external stimuli or internal thinking contents elicit shared DMN patterns. Compared to distraction, contents of thought are more individualized during rumination. Each individual has unique concerns or understanding of themselves or of negative events, and these thoughts depend on the novel materials generated by the MTL subsystem, which may be reflected by the lower consistency of activity across participants.

Reproducibility is a current major concern in functional MRI (35). Despite using multiple scanners and sites, our results still yielded a remarkable reproducibility. This consistency indicates that the effects we report are likely prominent and stable. Because rumination has long been deemed as an important phenomenological feature and risk factor for MDD (4), our findings may yield neuroimaging biomarkers of this common and disabling psychiatric condition.

It should be noted that our results were exclusively based on a young healthy adult sample and cannot be generalized to clinical MDD patients. Future studies should be conducted with clinical samples to obtain a full understanding of the pathological role of rumination in MDD.

In summary, with repeated measures, we discerned more nuanced and dissociated DMN network underpinnings of rumination. Our current results offer direct evidence on how DMN regions synchronize within and among subjects to underlie rumination, thus shedding new light on understanding the complex relationship between rumination and DMN abnormalities in MDD patients.

Materials and Methods

Participants

We recruited 42 young healthy adult participants from the community. One participant dropped out, leaving a final sample of 41 (22 females; mean age = 22.7 ± 4.1 years; 40 right-handed and one left-handed) subjects. The current study was approved by the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences. All participants gave informed consent.

Experimental procedure

A few days before the first scan, participants were invited to take part in an interview. During the interview, they first generated key words for individualized negative autobiographical events, then pre-experienced the rumination induction task. They also filled out a series of scales. For more details about the experimental procedure, see Introduction and SI text.

MRI data analysis

Data preprocessing was done with Data Processing Assistant for Resting-State fMRI (DPARSF, SI text) (49). A well-established atlas of regions of interest (ROIs) which is based on the 17-network parcellation derived from the fMRI data of 1000 healthy young adults (50) was used. The present study focused on the 24 regions belonging to the DMN. These regions can be further divided into 3 subsystems. The average timeseries were extracted from each of these ROIs. We first calculated the pair-wise Pearson correlation (z-transformed) among all ROIs, then averaged the correlations pairs within each subsystem or between subsystems as within and between subsystem FC. Paired t tests were performed to compare FC differences within or between subsystems, including head motion as a covariate. We used FDR correction to control false positive rates due to multiple comparisons. For each ROI, the ISC was calculated as the Z transformed Pearson correlation between one subject's time course and the average time course of all other subjects (31). Then we averaged the ISCs across DMN and its subsystems to get network's ISC. Paired t tests were conducted to compare between rumination and distraction states (For more details, see SI text).

Acknowledgments

This work was supported by the National Key R&D Program of China (2017YFC1309902), the National Natural Science Foundation of China (81671774, 81630031), the Hundred Talents Program and the 13th Five-year Informatization Plan (XXH13505) of Chinese Academy of Sciences, Beijing Municipal Science & Technology Commission (Z161100000216152). The authors appreciate the editorial assistance and support of Dr. Francisco X. Castellanos and would like to thank Dr. Men Weiwei for his technical support during data collection.

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Figure legends

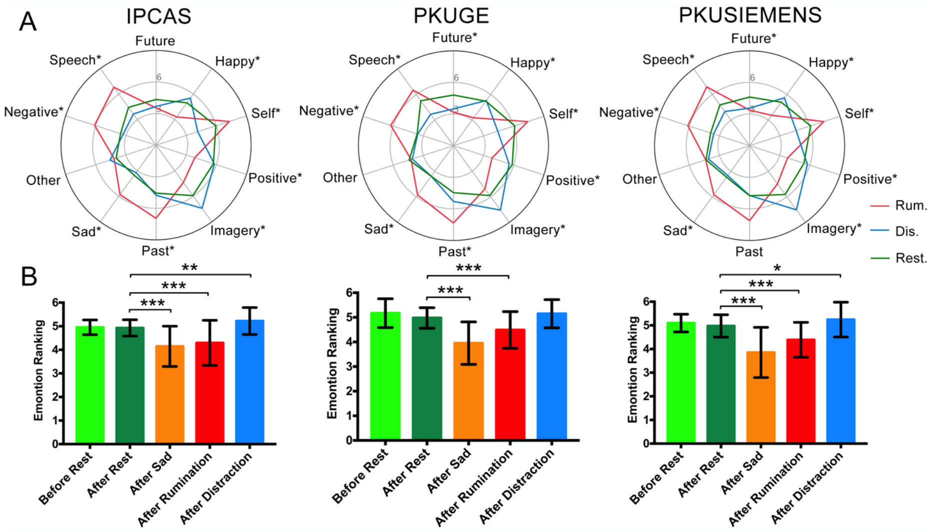

Figure 1. Self report behavior results. A) the form and content of thinking during rumination, distraction and resting states. Each axis stands for one dimension. *: significantly different among 3 states, p < 0.05, Bonferoni corrected. B) the emotional ratings (happy vs. unhappy) before resting state and after each states. *: p < 0.05; **: p <0.01; ***: p < 0.001.

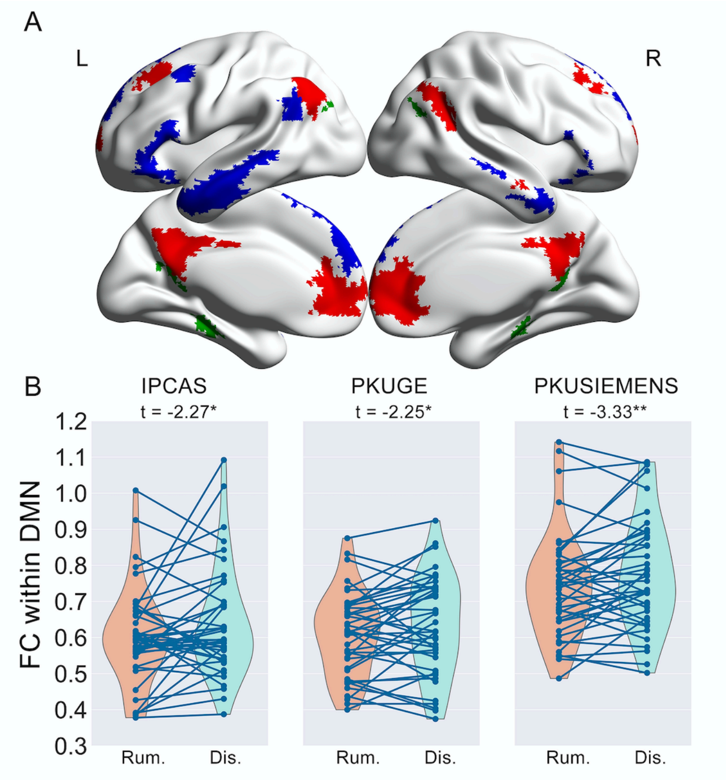

Figure 2. The differences of DMN FCs between rumination and distraction state across all 3 scanners. A) the DMN atlas used in the present study. Red: core subsystem; Blue: DMPFC subsystem; Green: MTL subsystem. L: left hemisphere; R: right hemisphere. B) Overall FC differences within DMN between rumination and distraction. *: $p < 0.05$; **: $p < 0.01$. Rum.: rumination state; Dis.: distraction state.

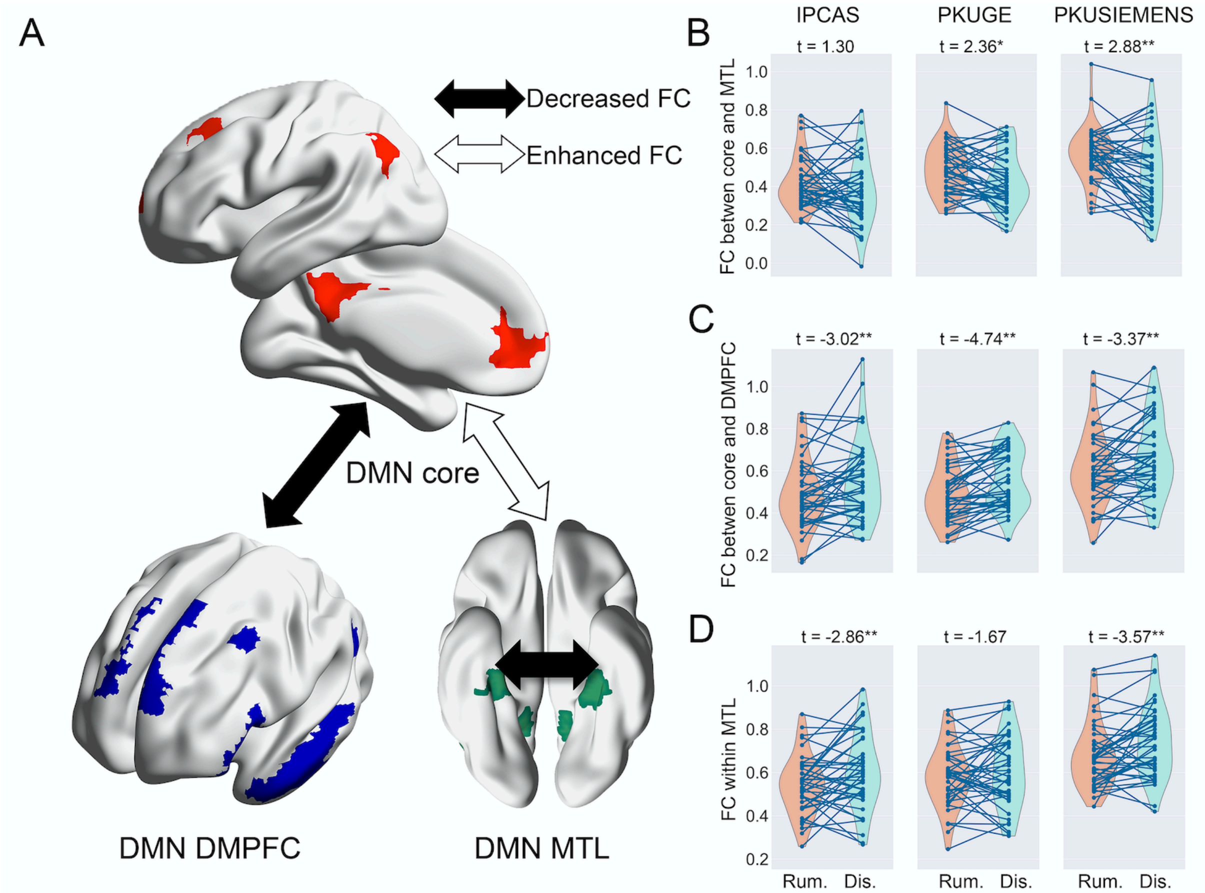

Figure 3. Differences of FCs among DMN subsystems between rumination and distraction state. A) Illustration of FC differences among DMN subsystems. B) An enhanced FCs between core and MTL subsystem in rumination state as compared to distraction state. C) Decreased FC between core and DMPFC subsystem in rumination state as compared to the distraction state. D) FC within MTL subsystem of DMN is decreased in rumination state as compared to distraction state. Note the reproducibility through all 3 scanners of these findings. **: significant after Bonferroni correction; *: significant uncorrected.

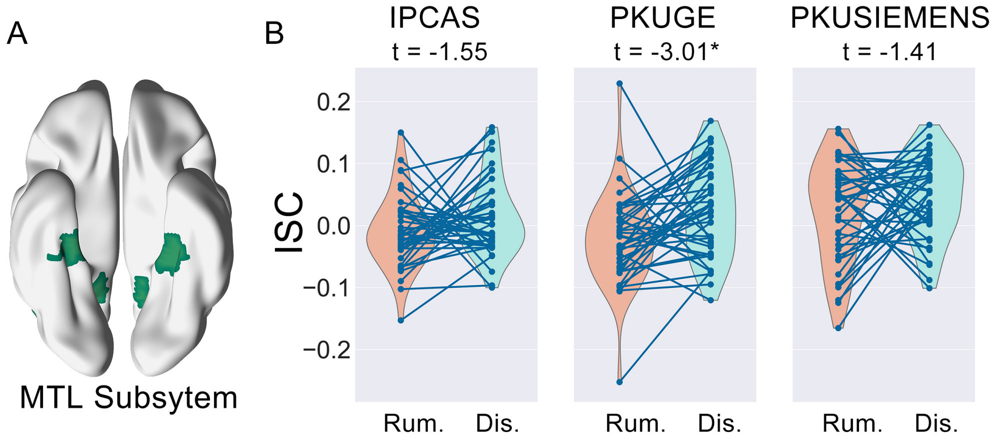

Figure 4. Inter-subject correlation (ISC) difference of MTL subsystem between rumination and distraction states. A) illustration of the MTL subsystem ROIs. B) Decreased ISC within the MTL subsystem. *: statistically significant.