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ARTICLE

Sex-specific resting state brain network dynamics in patients with major depressive disorder

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Sex-specific neurobiological changes have been implicated in Major Depressive Disorder (MDD). Dysfunctions of the default mode network (DMN), salience network (SN) and frontoparietal network (FPN) are critical neural characteristics of MDD, however, the potential moderating role of sex on resting-state network dynamics in MDD has not been sufficiently evaluated. Thus, resting-state functional magnetic resonance imaging (fMRI) data were collected from 138 unmedicated patients with first-episode MDD (55 males) and 243 healthy controls (HCs; 106 males). Recurring functional network co-activation patterns (CAPs) were extracted, and time spent in each CAP (the total amount of volumes associated to a CAP), persistence (the average number of consecutive volumes linked to a CAP), and transitions across CAPs involving the SN, DMN and FPN were quantified. Relative to HCs, MDD patients exhibited greater persistence in a CAP involving activation of the DMN and deactivation of the FPN (DMN + FPN-). In addition, relative to the sex-matched HCs, the male MDD group spent more time in two CAPs involving the SN and DMN (i.e., DMN + SN- and DMN-SN +) and transitioned more frequently from the DMN + FPN- CAP to the DMN + SN- CAP relative to the male HC group. Conversely, the female MDD group showed less persistence in the DMN + SN- CAP relative to the female HC group. Our findings highlight that the imbalance between SN and DMN could be a neurobiological marker supporting sex differences in MDD. Moreover, the dominance of the DMN accompanied by the deactivation of the FPN could be a sex-independent neurobiological correlate related to depression.

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INTRODUCTION

Major depressive disorder (MDD) is a prevalent psychiatric disorder with higher prevalence in females than males [1]. Sex differences in depressive symptoms, comorbidity and antidepressant efficiency in MDD are also commonly reported [2]. These possible sex differences in MDD have spurred interest in uncovering the potential sex-specific neural underpinnings of MDD. Emerging preclinical evidence shows that neurobiological abnormalities may differ between males and females with MDD [3, 4]. Sex-specific findings have emerged from neuroimaging studies in MDD [5–8], predominantly in limbic/striatal-prefrontal regions. Our prior study found that only female MDD patients exhibited atypical hyperactivity of limbic and striatal regions when experiencing psychosocial stress [9]. Another recent structural study revealed lower surface area in the ventrolateral prefrontal cortex, and lower cortical volume in the rostromedial prefrontal cortex, in female MDD patients compared to healthy females, whereas the male MDD patients showed opposite structural patterns when compared to healthy males [6]. Collectivity, prior neuroimaging findings thus revealed that sex-specific neural mechanisms in MDD do not only pertain to the magnitude, but also to the direction of the effects, highlighting the need for comprehensive investigations. However, this has not yet been achieved, particularly regarding sex-specific alterations in large-scale resting-state neural networks [10].

Mounting evidence suggests that MDD patients are characterized by a dysfunction of several large-scale networks [i.e., default mode network (DMN), frontoparietal network (FPN) and salience network (SN)]. The most common outcome is that individuals with MDD exhibit hypoconnectivity within the FPN [11, 12], hyperconnectivity within the DMN [13], and hyperconnectivity between the DMN and FPN [12]. Of note, hypoconnectivity within the DMN has been reported among patients with recurrent episodes [14], suggesting that the trajectory of MDD-related DMN alterations may change with increasing number of major depressive episodes. Moreover, in healthy individuals, sex differences in network organization were also observed in terms of DMN, SN and FPN, with emerging evidence suggesting that females display more intra-network connectivity, while males exhibit more inter-network connectivity [15, 16], implicating potential sex differences in information processing.

Critically, few studies have evaluated the role of sex assigned at birth on large-scale functional brain network alterations in MDD. One amygdala-based functional connectivity (FC) study found that

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compared to healthy peers of the same gender, females with depressive symptoms had greater amygdala FC with the insula and the mid-posterior cingulate cortex (PCC), whiles males with depressive symptoms showed weaker FC between the amygdala and subcallosal prefrontal cortex [17]. Another FC study found that males with MDD exhibited increased anterior cingulate FC with the PCC and decreased anterior cingulate FC with the anterior insula, temporal pole, and lateral prefrontal cortex; this study also revealed within-DMN hyperconnectivity in males with MDD, whereas females with MDD featured a modest within-DMN hypoconnectivity [18]. Together, these findings thus highlight increased functional coupling within the DMN and decreased functional coupling between the SN and DMN in males with MDD relative to healthy males, as well as modestly decreased functional coupling within the DMN and increased functional coupling between the SN and DMN in females with MDD relative to healthy females.

One potential limitation of previous work probing sex-specific brain network mechanisms in MDD pertains to the focus on *static* functional network properties. *Dynamic* network analytical techniques capture changes in functional coordination among distributed brain regions over time [19–21], which is likely important regarding functional network alterations in MDD. Relatedly, one study comparing statistical models involving static *versus* dynamic functional network properties found that the latter enabled better MDD identification [22]. Several studies have examined brain dynamics in MDD without probing potential sex differences using co-activation pattern (CAP) analysis [23, 24], which parses resting-state data into CAPs and allows for the computation of several network properties. One CAP study in adolescents found that higher levels of depressive symptoms severity was associated with greater expression and larger persistence of a frontoinsular-DMN CAP and more transitions between this network and a canonical DMN network [24]. Additionally, adult females diagnosed with MDD spend more time in an FPN-posterior DMN CAP and transition more frequently between this CAP and a canonical DMN CAP [23]. These reports revealed that MDD patients may exhibit atypical functional coordination within the DMN and between the FPN and DMN, which supports prior findings observed in MDD using static FC. However, sex-specific resting-state network dynamics in MDD have not been sufficiently evaluated.

Here, we tested sex differences in resting dynamic functional network properties in a relatively large sample of male and female (sex assigned at birth) healthy controls and first-episode unmedicated MDD patients using a data-driven CAP approach [25, 26]. Since prior static FC analyses revealed sex-specific functional coupling among SN and DMN regions (i.e., males with MDD exhibited greater within-DMN FC and lower SN-DMN FC relative to male HCs; females with MDD exhibited lower within-DMN FC and greater SN-DMN FC), we speculated that male and female MDD patients would exhibit distinct CAP properties (i.e., time spent and persistence) in CAPs involving the SN and DMN. Specifically, the female MDD patients would spend less time/persist less in CAPs involving the coactivation of DMN regions or an opposite polarity between SN and DMN regions (since the SN and DMN are anti-correlated in the resting-state as revealed by static FC), whereas the male MDD patients would spend more time/persist more in these same CAPs.

MATERIALS AND METHODS

Participants

Patients meeting DSM-IV-TR Axis I disorders criteria for their first episode were recruited, with exclusion criteria for potential confounding effects of antidepressant medications, multiple episodes, and comorbidities (see *Supplemental Methods* for details). All participants were aware of the study's purpose and provided informed written consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Second Xiangya Hospital of Central South University. Fourteen MDD patients and 22 HCs were excluded because of excessive head movement (see fMRI Preprocessing for details), leaving 243 HCs (137 female) and 138 MDD (83 female) patients for analysis. Clinical and demographic characteristics of MDD patients and HCs are summarized in Table 1 and *Supplemental Results*.

fMRI acquisition

All scans were collected on the same 3 T Siemens Magnetom Skyra scanner (Siemens Healthineers, Erlangen, Germany) with a 16-channel head coil. Resting-state fMRI data were collected with an echo-planar imaging sequence and repetition time/echo time = 2000/30 ms, thickness/gap = 4/1 mm, field of view = 256 mm^2, flip angle = 80°, matrix = 64 × 64, 32 slices. During the resting-state fMRI scan, participants were instructed to rest with their eyes closed without falling asleep. After finishing the scan, they were asked whether they stayed awake; only the data of subjects who stayed awake were considered for analysis. The total acquisition time for the resting-state fMRI data was 7 min 12 s (216 volumes).

fMRI preprocessing

Preprocessing was performed using fMRIPrep 1.5.8 [27], which is based on Nipype 1.4.1 [28]. We outline the main steps below (see *Supplemental Methods* for details). Following the removal of the first four volumes, realignment, slice-time correction, co-registration to the structural image and segmentation, blood oxygenation level-dependent (BOLD) time-series were resampled into MNI space, and spatially smoothed with a Gaussian kernel (6 mm full width at half-maximum). Independent component analyses (ICA-AROMA, [29]) were then conducted to identify and exclude motion artifacts. Lastly, the denoised BOLD time-series were high-pass filtered ($f = 0.0067$ Hz). Subjects were excluded if they had more than 20% of resting-state volumes with at least 0.5 mm framewise displacement (FD) and/or 1.5 standard deviation temporal derivative of timecourses of root mean square variance over voxels (DVARS).

Resting-state Co-activation Pattern (CAP) analysis

An ROI-wise seed-free whole-brain co-activation pattern analysis was conducted using custom scripts originating from the *TbCAPs* toolbox [26]. First, timecourses were extracted for each participant using 349 ROIs consisting of cortical (333) and subcortical (16) regions [30]. Second, consensus clustering was performed across the whole dataset to determine the optimal number of CAPs, which involves running *k*-means clustering over several folds on a randomly selected subsample of the data without replacement over the specified *k* range. A good clustering solution is one for which across folds, two volumes (one pair) are either always clustered together or never clustered together. The proportion of ambiguously clustered pairs (PAC) was used to quantify the quality of consensus clustering, with lower PAC values indicating more robust clustering. In the current study, *k*-means clustering was run over 50 folds on a randomly selected 80% subsample of the whole dataset for $k = 2$ to 20. The optimal PAC value was achieved for $k = 10$ (see Supplementary Fig. S1). Finally, *k*-means clustering using the cosine distance and random initialization of the algorithm (50 replicates) was run to partition all volumes into 10 CAPs.

Considering the hypothesis of the current study, four CAPs involving the DMN, FPN and SN (CAP_4, CAP_6, CAP_7, CAP_8) were included in the group analyses on CAP metrics (they are shown in Fig. 1). CAP_4 (DMN + SN-) involved activation of the DMN and deactivation of SN regions. CAP_6 (DMN-SN +) included activation of SN regions and deactivation of DMN regions. CAP_7 (DMN + FPN-) involved activation of DMN regions and deactivation of FPN regions. Finally, CAP_8 (DMN-FPN +) was characterized by activation of FPN regions and deactivation of anterior DMN regions. See *Supplemental Information* and Supplemental Fig. S2 for a detailed description of other CAPs. Two CAP metrics were calculated for each CAP of interest: time spent in CAP (total number of volumes spent in each CAP throughout the scan) and persistence (average total number of consecutive volumes participants remained in a given CAP). Transitions (total number of transitions from one CAP to another) were only calculated for CAPs exhibiting significant group effects. All CAP variables were inspected for normality or outliers (values outside the 1st quartile ± 3 × interquartile range), and any variables that violated assumptions were square root-transformed (see Supplementary Table S1 for the descriptive statistics of all CAPs).

Group-level analysis

Group differences on time spent, persistence and number of transitions. With the aim to examine group differences in time spent and persistence in each hypothesized CAP, a series of *Diagnosis* (MDD/HC) × *Sex* (male/female) ANCOVAs were conducted with age as a covariate for each CAP metric (i.e., time spent, persistence) with only CAPs involving SN, DMN and FPN networks. False discovery rate (FDR) correction was applied for multiple ANCOVAs for each effect (i.e., *Diagnosis*, *Sex*, *Diagnosis* × *Sex* interaction) in each metric (i.e., time spent, persistence). For the CAPs showing group effects in terms of either time spent or persistence, numbers of transitions were calculated and compared across groups using *Diagnosis* (MDD/HC) × *Sex* (male/female) ANCOVAs controlling for age. *Post-hoc* simple effects analyses (with Bonferroni correction) were conducted for significant *Diagnosis* × *Sex* interaction effects.

RESULTS

Group differences in time spent in CAP and CAP persistence

For the "time spent in CAP" metric, a significant *Sex* × *Diagnosis* interaction emerged in CAP_4 [DMN + SN-] ($F_{(1,376)} = 8.96$, $p_{FDR} = 0.012$, $\eta^2 = 0.023$) and CAP_6 [DMN-SN +] ($F_{(1,376)} = 5.54$, $p_{FDR} = 0.038$, $\eta^2 = 0.015$). For CAP_4 [DMN + SN-], upon follow-up simple effect analyses, time spent was greater in the male MDD group compared to the male HC group ($p_{Bonferroni} = 0.034$; Fig. 2A); additionally, time spent was also greater in the female HC group relative to the male HC group ($p_{Bonferroni} = 0.008$; Fig. 2A). For CAP_6 [DMN-SN +], follow-up simple effect analyses revealed greater time spent by the male MDD group in comparison to the male HC group ($p_{Bonferroni} = 0.01$; Fig. 2C). No other significant group effects emerged for time spent in the 4 CAPs of interest (all $p_{FDR} > 0.05$; Supplementary Table S2). In summary, the male MDD group spent more time in DMN + SN- and DMN-SN+ configurations relative to the male HC group, whereas female MDD patients did not exhibit these alterations.

For the persistence metric, a significant *Sex* × *Diagnosis* interaction in CAP_4 [DMN + SN-] emerged ($F_{(1,376)} = 9.21$, $p = 0.003$, $p_{FDR} = 0.012$, $\eta^2 = 0.024$). Follow-up simple effect analyses revealed lower persistence in the female MDD group relative to the female HC group ($p_{Bonferroni} = 0.029$) and the male MDD group ($p_{Bonferroni} = 0.039$; Fig. 2B). In addition, the female HC group exhibited greater persistence in CAP_4 [DMN + SN-] in comparison to the male HC group ($p_{Bonferroni} = 0.022$; Fig. 2B). For CAP_7 [DMN + FPN-], a significant main effect of *Diagnosis* emerged ($F_{(1,\ 375)} = 6.94$, $p = 0.009$, $p_{FDR} = 0.036$, $\eta^2 = 0.018$), with the MDD group exhibiting greater persistence than the HC group (Fig. 2D); additionally, a significant main effect of *Sex* also emerged ($F_{(1,\ 375)} = 6.77$, $p = 0.010$, $p_{FDR} = 0.040$, $\eta^2 = 0.018$), with the male group showing greater persistence relative to the female group. No other significant effects emerged for the 4 CAPs of interest (all $p_{FDR} > 0.05$; Supplemental Table S3). In summary, the MDD group showed greater persistence in a DMN + FPN- configuration relative to HCs; at the same time, females showed less persistence than males in a DMN + SN- configuration when suffering from MDD, while the opposite was seen for healthy subjects.

All *Diagnosis* × *Sex* interaction findings remained significant in supplementary analyses controlling for BDI scores and mean FD (Supplementary Table S4). Supplementary analyses were also conducted to test group differences on other CAPs that were not part of our a priori hypotheses (i.e., CAP_1, CAP_2, CAP_3, CAP_5, CAP_9, CAP_{10}; see Supplementary Table S5). Significant *Diagnosis* × *Sex* interactions emerged for time spent and persistence in CAP_2 (activation of visual network); see *Supplemental Results* for more details.

Follow-up analyses on group differences in number of transitions between CAP_4, CAP_6, and CAP_7

Four *Sex* × *Diagnosis* ANCOVA analyses with age as a covariate were conducted to test group differences in the number of

Table 1. Clinical and demographic characteristics of MDD patients and healthy participants.

Characteristics	HC Male	HC Female	MDD Male	MDD Female	Diagnosis		Sex		Diagnosis × Sex	
	($n = 106$)	($n = 137$)	($n = 55$)	($n = 83$)	F	p	F/t	p	F	p
Age (Years)	20.76 (2.92)	21.09 (3.32)	24.31 (4.76)	25.66 (7.79)	61.51	< 0.001	2.65	0.104	0.98	0.323
Education (Years)	14.33 (1.45)	14.63 (1.68)	14.38 (2.26)	13.95 (2.32)	2.39	0.123	0.10	0.753	3.15	0.077
Mean FD	0.12 (0.04)	0.12 (0.05)	0.11 (0.06)	0.13 (0.06)	0.19	0.660	6.61	0.011	1.94	0.164
Illness duration (Months)	-	-	12.66 (21.50)	9.35 (11.54)	-	-	1.03	0.307	-	-
BDI	5.6 (5.97)	5.65 (5.84)	26.89 (10.59)	30.80 (10.18)	754.98	< 0.001	5.47	0.020	5.23	0.023
HAM-D	–	–	19.96 (6.47)	22.69 (4.80)	–	–	−2.85	0.005	–	–

FD Framewise displacement, *BDI* Beck Depression Inventory, *HAM-D* Hamilton Depression Rating Scale, *HC* Healthy control, *MDD* Major depressive disorder.

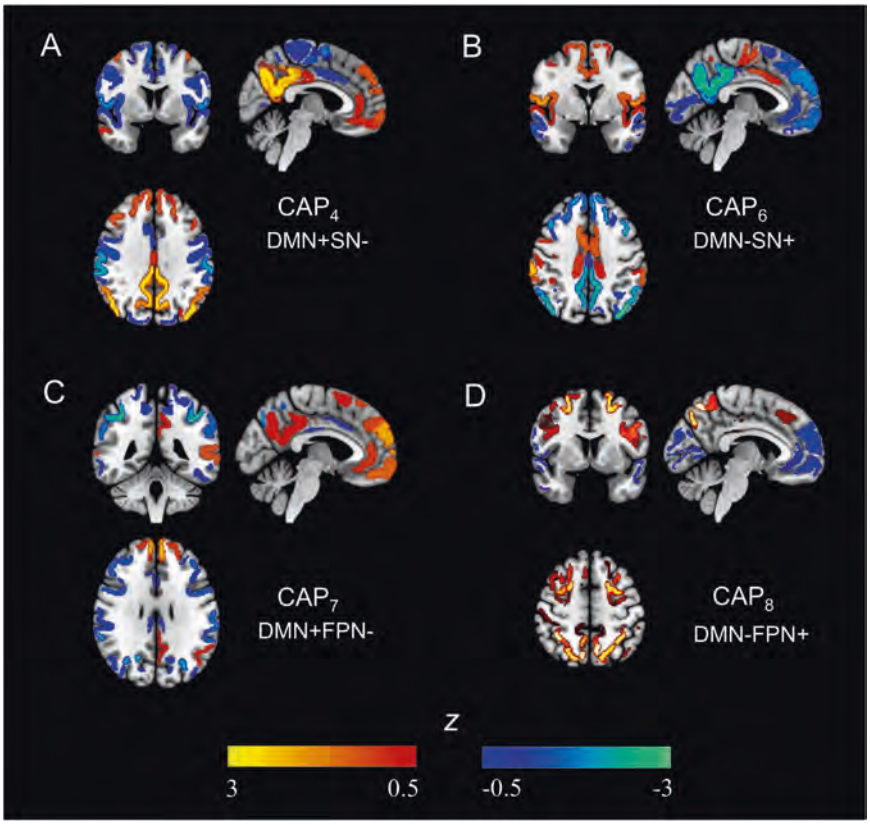

Fig. 1 Co-activation patterns (CAPs) of interest. Each CAP was characterized by the activation (see warm colors) and deactivation (cold colors) of brain regions. Z-scored CAPs are displayed at $0.5 \leq |Z| \leq 3.0$. **A** CAP_4 involving activations of DMN regions and deactivations of salience network regions. **B** CAP_6 involving activations of salience network regions and deactivations of DMN regions. **C** CAP_7 involving activations of DMN regions and deactivations of FPN regions. **D** CAP_8 involving activations of FPN regions and deactivations of anterior DMN regions. DMN Default mode network, FPN Frontoparietal network, SN Salience network.

transitions between CAP_4 [DMN + SN-] and CAP_7 [DMN + FPN-] as well as between CAP_6 [DMN-SN +] and CAP_7 [DMN + FPN-]. Since the mean number of transitions between CAP_4 [DMN + SN-] and CAP_6 [DMN-SN +] is almost equal to zero (see Supplementary Fig. S3), group comparison was not performed. Significant interactions emerged for transitions from CAP_7 [DMN + FPN-] to CAP_4 [DMN + SN-] ($F_{(1,374)} = 5.58$, $p = 0.017$, $p_{FDR} = 0.044$, $\eta^2 = 0.015$; Supplementary Table S6) and from CAP_6 [DMN-SN +] to CAP_7 [DMN + FPN-] ($F_{(1,373)} = 5.27$, $p = 0.022$, $p_{FDR} = 0.044$, $\eta^2 = 0.014$; Supplementary Table S6). In the former case, follow-up simple effect analyses revealed that the male MDD group exhibited a greater number of transitions in comparison to the male HC group ($p_{Bonferroni} = 0.010$; Fig. 3); the male MDD group also showed a greater number of transitions relative to the female MDD group ($p_{Bonferroni} = 0.040$; Fig. 3). In the latter case, none of the simple effect analysis findings survived multiple comparison correction (all $p_{Bonferroni} > 0.05$). No significant group effects on the number of transitions emerged for CAP_7 [DMN + FPN-] → CAP_6 [DMN-SN +] and CAP_4 [DMN + SN-] → CAP_7 [DMN + FPN-] cases (*i.e.*, opposite transitions; all $p_{FDR} > 0.05$). In summary, the male MDD group specifically transitions more frequently from a DMN + FPN- to a DMN + SN- configuration.

Associations between resting dynamic metrics and clinical measures

No significant associations were observed between resting dynamic metrics exhibiting significant group differences and clinical measures (all $p_{FDR} > 0.05$). See *Supplemental Methods and* Supplemental Table S7 for details.

DISCUSSION

The overarching goal of the current study was to test the potential interaction between MDD and sex assigned at birth on resting-state brain network dynamics. Our findings revealed that MDD patients (irrespective of sex) spent more time in one CAP involving activation of the DMN and deactivation of the FPN (DMN + FPN-) when compared to HCs. In addition, we also unraveled potential sex-specific effects in CAPs involving the SN, DMN and FPN in MDD. Specifically, males with MDD spent more time in CAPs involving the SN and DMN (DMN + SN-/DMN-SN +) relative to male HCs, whereas females with MDD exhibited greater persistence in a DMN + SN- CAP relative to female HCs; moreover, the male MDD group exhibited a greater number of transitions from the DMN + FPN- CAP to the DMN + SN- CAP relative to the male HCs and female MDD group. Collectively, these findings highlight the importance of considering sex as a variable when exploring the neural underpinnings of MDD and provide evidence of potential sex-specific brain network dynamic alterations in MDD.

The current findings revealed that MDD patients, irrespective of sex, exhibited greater persistence in a DMN + FPN- CAP compared to HCs [31]. Consistently, a CAP study also found that time spent in a DMN + FPN- CAP was positively associated with depressive symptom severity [32]. The DMN is related to self-referential mental activity, and the FPN is crucial for goal-related behavior and emotion regulation [10]. Thus, the longer persistence in a DMN + FPN- CAP observed in MDD could reflect a dysfunction of shifting the attention from self-referential thoughts to goal-related behavior. Relatedly, other studies have found that individuals with MDD spend more time and/or persist longer in mixed CAPs involving the DMN, including a frontoinsular-DMN CAP in a largely

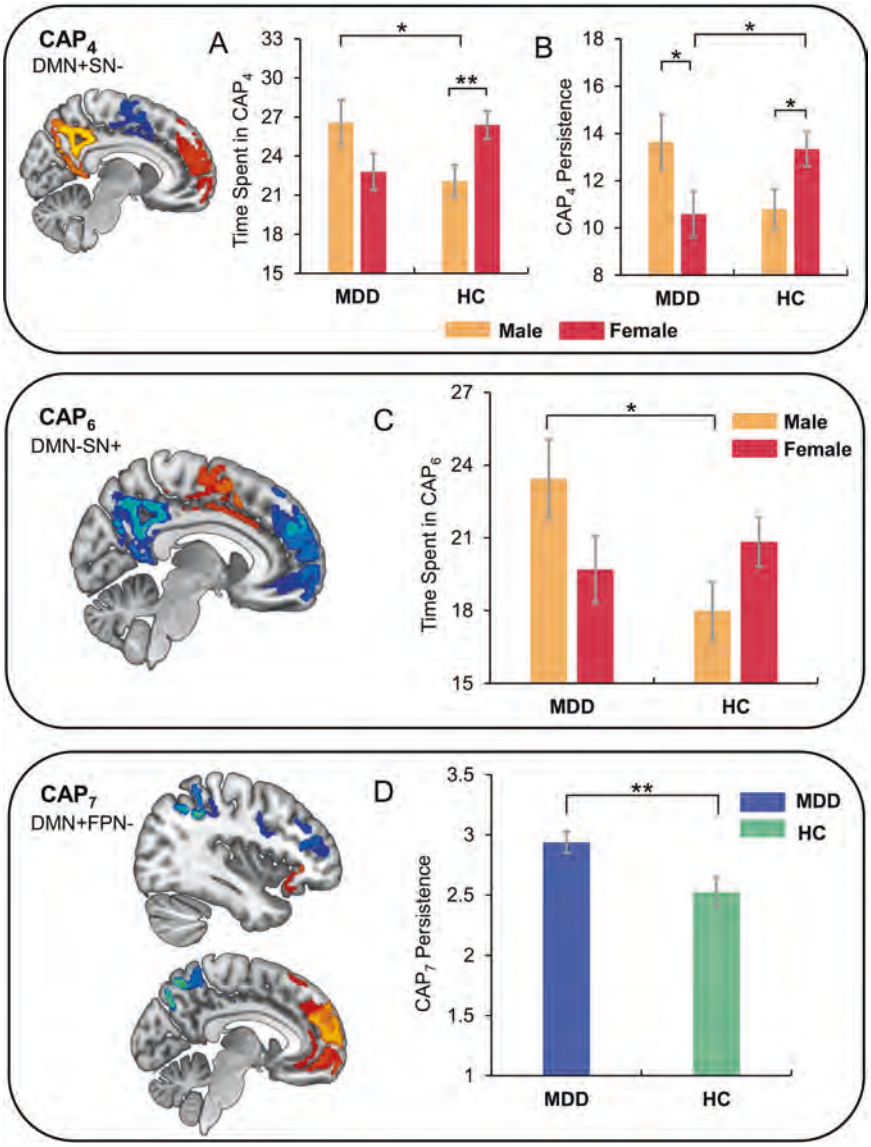

Fig. 2 Group differences on time spent in CAPs and persistence. A significant *Diagnosis* × *Sex* interaction effect emerged for the time spent (**A**) and persistence (**B**) of CAP_4 [DMN + SN-]. Follow-up analysis revealed a greater time spent in the CAP for the male MDD group compared to the male HC group, while the female MDD group showed lower persistence relative to the female HC group; in addition, time spent and persistence measures were also larger in the female HC group relative to the male HC group, and persistence was lower in the female MDD group relative to the male MDD group. **C** A significant *Diagnosis* × *Sex* interaction effect emerged for the time spent in CAP_6 [DMN-SN +] involving activations of SN regions and deactivations of DMN regions. Follow-up analysis found that the male MDD group spent more time in this CAP relative to the male HC group, whereas the female MDD group did not show significant alterations. **D** The MDD group exhibited higher persistence in CAP_7 [DMN + FPN-] involving activations of DMN regions and deactivations of FPN regions in comparison to the HCs. CAP co-activation pattern, DMN Default mode network, FPN Frontoparietal network, SN Salience network, HCs Healthy controls, MDD Major depressive disorder. Estimated means are plotted, and error bars represent standard error (SE). $^{*}p < 0.05$, $^{**}p < 0.01$.

medicated adolescent MDD sample [24] and an FPN-PCC CAP (activation of PCC and FPN) in an unmedicated adult female sample [23]. Together, these findings suggest that DMN dominance and altered DMN-FPN interactions could be a core neurobiological feature of MDD.

Consistent with our hypothesis, more time spent in CAPs (DMN + SN-, DMN-SN +) exhibiting an opposite polarity between the SN and DMN, and a higher number of transitions from the DMN + FPN- to the DMN + SN- CAP, were observed in males, whereas lower persistence in the DMN + SN- CAP was observed in females. These findings agree with prior literature showing weaker static FC between SN- and DMN-related regions in males with depressive symptoms and greater FC between SN- and DMN-related regions in female MDD patients [17, 18]. The current study further supports the sex-specific SN and DMN coupling alterations in MDD using a dynamic resting-state approach and provide new insights into the sex-specific SN and DMN coupling in MDD. To supplement these findings, we also quantified group differences in static FC between the SN and DMN (see more details in Supplementary Methods and Results; Supplementary Table S8); a trend of significant Diagnosis × Sex interaction was observed, which further supports CAP findings. Static FC averages together different contributions, which may make it less sensitive to detecting group differences in terms of between-network coordination relative to the dynamic FC approach.

Our findings revealed sex-specific functional coordination among SN- and DMN-related brain regions in MDD. The SN mainly plays a role in salience detection, and the DMN in self-

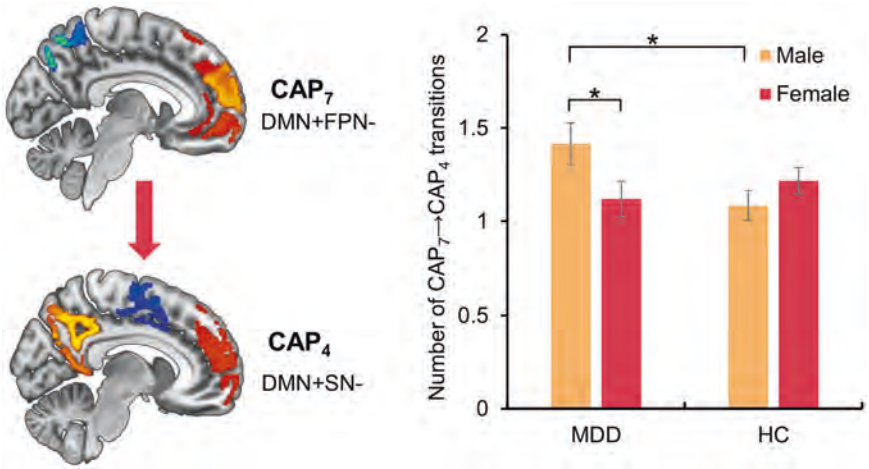

Fig. 3 Group differences on transition probability from CAP_7 to CAP_4. A significant *Diagnosis* × *Sex* interaction emerged for the number of transitions from CAP_7 [DMN + FPN-] to CAP_4 [DMN + SN-]. Follow-up simple effect analyses revealed that the male MDD group exhibited a significantly higher number of transitions from CAP 7 to CAP 4 relative to the female MDD group and the male HC group, whereas the female MDD group did not exhibit significant alterations relative to HCs. DMN default mode network, FPN frontoparietal network, SN salience network. Estimated means are plotted, and error bars represent standard error (SE). *$p < 0.05$.

referential processing [33]. For HCs, females spent more time and persisted more in the DMN + SN- CAP (and a similar trend was observed for the DMN-SN + CAP) relative to males. A prior study also found that females persisted longer in certain CAPs and switched less frequently, showing a less flexible functional substrate whereas the males exhibited higher dynamic fluidity [34]. Our findings complement the existing literature and highlight this pattern specifically for SN/DMN functional coordination. Less time in and persistence of CAPs exhibiting an opposite polarity between two networks relative to externally focused attention and self-focused processes in the male HCs could be beneficial to quick problem solving. In line with this, one prior study found that less persistence (higher dynamic fluidity) in CAPs was associated with males' higher abilities in problem solving [34]. For females, higher persistence in a DMN + SN- configuration in the resting-state could be adaptive for reducing attention to external stimulus as well as external stimulus induced-rumination. Together, we could speculate that either the lower time spent/persistence in males or greater time spent/persistence in females is adaptive.

Following this reasoning, it is then reasonable why opposite patterns were observed in male and female MDD patients in CAPs exhibiting an opposite polarity between the SN and DMN: it is more likely a collapse of their original adaptive spontaneous functional substrate. Stress is a well-acknowledged casual factor of MDD [35]; overwhelming stress contributing to the onset of MDD could damage/reverse the resting functional substrates beneficial to stress adaptation in a sex-dependent way. However, these speculations need to be further verified. Noteworthily, our current findings reinforced the concern that similar neural substrates could contribute to distinct depressed conditions in males as opposed to females. For instance, in the current study, male MDD patients exhibited similar CAP patterns to female HCs although they also displayed significant differences in depressive severity. These findings highlight the importance of clarifying the sex-specific neural mechanisms of depression, which could provide guidance for precision treatment, especially for region-targeted neuromodulation therapy. Together, our results highlight that the SN and DMN interactions could be key neuroimaging markers for distinguishing male and female MDD patients and also point to putative neural targets to explore factors contributing to sex-specific effects in MDD.

Several limitations should be mentioned. First, our depressed sample consisted of first-episode medication-naive individuals with MDD and no comorbidities, which may make it less representative of the whole community. Replication of the current findings in a clinically more heterogeneous sample is needed. Second, lack of group matching for age required entering age as a covariate in the analyses. Third, the current female MDD group had more severe depressive symptoms than the male MDD group; nevertheless, the *Sex* × *Diagnosis* interaction was confirmed when controlling for depressive severity (see Supplementary Table S4 for details). Fourth, we analyzed effects of sex assigned at birth. However, sex effects are often distributional and overlap [36]. In addition, this study does not consider gender identity and associated environmental impact. Fifth, the relatively small number of per-subject volumes and the usage of a 16-channel head coil may affect the effectiveness of the CAP approach; further replication of the current findings is thus warranted. Sixth, the extraction of CAPs does not prove non-stationarity in the data, or the existence of a state-based data organization. Indeed, approximately similar CAPs and metrics of temporal dynamics can be obtained from a static null model with identical power distribution and covariance structure as the original data [37], CAPs should thus strictly be regarded as momentary co-activation patterns. Seventh, CAP analysis operates under the limiting assumptions of (1) a shared pool of CAPs across all subjects from the analyzed population, and (2) the expression of just one CAP at each moment in time. While similar assumptions are made in other popular dynamic fMRI analytical approaches [38, 39], there are also alternatives that work under different assumptions, such as through first-order autoregressive models [39] or the extraction of co-activation patterns that can overlap not only spatially, but also in temporal expression [40]. Here, we chose CAP analysis because (1) it enables a frame-wise analysis, (2) it shows direct links to the well acknowledged whole-brain and seed-based static FC approaches, and (3) it has been leveraged in several past reports investigating MDD [23, 41], easing cross-study interpretations.

Despite several limitations, to the best of our knowledge, the current study is the first to investigate the potential interaction between sex and MDD psychopathology in terms of resting-state brain dynamics. Both male and female MDD patients spent more time in a CAP involving the activation of DMN regions and deactivation of FPN regions during the resting-state, which provides evidence for a general (sex-nonspecific) neural abnormality related to depression. In addition, male and female MDD patients exhibited sex-specific neurobiological features in resting-state CAPs involving the SN and the DMN, highlighting the critical

role of SN and DMN interactions in distinguishing between the male and female MDD patients and providing evidence for sex differences in the psychopathology of depression.

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AUTHOR CONTRIBUTIONS

SY, ELB, DAP, and XW conceptualized the study; SY, XW, DD, XZ, CL, XS, GX, and CC collected the data; DD, ELB, TAWB, DAP, and MI analyzed the data and interpreted the data. DD drafted the manuscript with critical revisions from ELB, DAP, TAWB, and MI. All authors approved the final manuscript and are accounted for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS

Over the past three years, Dr. Pizzagalli has received consulting fees from Albright Stonebridge Group, Boehringer Ingelheim, Compass Pathways, Engrail Therapeutics, Neumora Therapeutics (formerly BlackThorn Therapeutics), Neurocrine Biosciences, Neuroscience Software, Otsuka, Sunovion, and Takeda; he has received honoraria from the Psychonomic Society and American Psychological Association (for editorial work) and from Alkermes; he has received research funding from the Brain and Behavior Research Foundation, Dana Foundation, Millennium Pharmaceuticals, and Wellcome Leap; he has received stock options from Compass Pathways, Engrail Therapeutics, Neumora Therapeutics, and Neuroscience Software. There are no

conflicts of interest with the work conducted in this study. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. The other authors report no financial relationships with commercial interests.

ADDITIONAL INFORMATION

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Sex-specific Resting State Brain Network Dynamics in Patients with Major Depressive Disorder

Supplemental Information

Supplemental Methods

Participants

Patients with an MDD diagnosis were recruited from the clinical outpatient of the Second Xiangya Hospital affiliated with Central South University. Healthy participants were recruited from two colleges and the community through advertisements and posters. Clinical assessments were conducted by two psychiatrists using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition [1]. In addition, the Beck Depression Inventory-II (BDI) [2] and the 17-item Hamilton Depression Rating Scale [3] were administered to assess severity of depressive symptoms among patients with major depressive disorder (MDD). Healthy controls had to be free of current psychiatric disorder diagnoses. Additionally, for both depressed patients and healthy controls, the exclusion criteria were: 1) prior DSM-IV-TR disorder; 2) history of antidepressant use or psychotherapy; 3) history of alcohol/substance abuse; 4) other DSM-IV-TR Axis I disorders comorbid; and 5) neurological disorder diagnosis, structural brain abnormality, or MRI contraindication.

Data Preprocessing

Preprocessing was performed using fMRIPrep 1.5.8 [4,5] which is based on Nipype 1.4.1 [6,7]. *Details of the standardized pipeline below were automatically generated by fMRIPrep to maximize replicability of the preprocessing* [4].

Anatomical Data Preprocessing

T1-weighted (T1w) images were corrected for intensity non-uniformity with N4BiasFieldCorrection [8] distributed with ANTs 3.0.0 [9], and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 6.0.0, RRID:SCR_002823, [10]). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1,

RRID:SCR_001847, [11]) , and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, [12]). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 3.0.0), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c[[13], RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model [[14], RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym].

Functional Data Preprocessing

For each of the three BOLD runs, the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. A deformation field to correct for susceptibility distortions was estimated based on fMRIPrep's fieldmap-less approach. The deformation field resulted from the co-registration of the BOLD reference to the same-subject T1w-reference with its intensity inverted [15,16]. Registration was performed with antsRegistration (ANTs 3.0.0), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template [17]. Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration [18]. Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using mcflirt (FSL 6.0.0, [19]). BOLD runs were slice-time corrected using 3dTshift from AFNI 20190007 ([20], RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD

time-series are referred to as preprocessed BOLD in original space, or just preprocessed BOLD. Motion artifacts were identified using independent component analysis (ICA-AROMA, [21]) and subsequent visual inspection of ICA components was performed using regfilt (FSL) on the preprocessed BOLD in MNI space (MNI152NLin6Asym) time-series after removal of non-steady volumes (first 4 volumes) and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full width at half-maximum). The BOLD time-series were resampled into MNI152NLin6Asym standard space using antsApplyTransforms (ANTs 3.0.0). Finally, the denoised BOLD runs were temporally filtered using a high bandpass of 150 sec. Subjects were excluded if they had more than 20% trials with 0.5 mm movement based on framewise displacement (FD) and/or 1.5 standard temporal derivative of timecourses of RMS variance over voxels (DVARS). Fourteen MDD patients and 22 HCs were excluded because of excessive head movement.

Group-level Analysis on Co-activation Characteristics

With the aim to replicate the co-activation characteristics found by prior studies: 1) CAPs are grouped into several pairs with opposite spatial co-activation patterns [22,23]; 2) members of a pair with opposite spatial co-activation patterns rarely transition to each other [22,23]. Pearson correlation analyses were conducted to assess spatial similarity between CAPs, and the number of transitions between CAPs was also calculated.

In addition, a series of *Diagnosis* (MDD/HC) × *Sex* (male/female) ANCOVAs were conducted with age as a covariate for each CAP metric (i.e., time spent, persistence) with CAPs which were not selected (CAP_1, CAP_2, CAP_3, CAP_5, CAP_9, CAP_{10}) in the current study.

ROI-wise FC analysis among SN, DMN and FPN

To supplement the CAP results, ROI-wise FC analysis was conducted. First, regional BOLD timecourses were extracted for each subject using 349 ROIs (same parcellation as for CAP analysis), consisting of cortical and subcortical regions. Second, Pearson's correlation coefficients were quantified and Fisher's z-transformation was applied to generate a correlation z-matrix for each subject using the DPARSF toolbox (http://rfmri.org/DPARSF, [24]). Third, mean FC values within and between our three networks of interest (i.e., mean SN FC, mean DMN FC, mean FPN FC, mean DMN-FPN FC, mean DMN-SN FC, mean SN-FPN FC) were

calculated for each subject. Regions of interest for the SN, DMN and FPN were identified by the Gordon parcellation [25] generated from resting-state FC correlations.

For the group-level analysis, a series of *Diagnosis* (MDD/HC) × *Sex* (male/female) ANCOVAs were conducted with age as a covariate for the mean static FC within and between the three networks.

Correlation Analysis

Pearson correlation analyses between CAP metrics (i.e., time spent, persistence and number of transitions) exhibiting MDD-related effects and the BDI score were conducted in male and female MDD groups separately.

To connect traditional static FC with the resting brain dynamics metrics among the SN, DMN and FPN networks, Pearson correlation analyses were conducted among these metrics across all subjects.

Supplemental Results

Demographic and clinical characteristics

The clinical and demographic characteristics of the four groups are summarized in Table 1. The MDD group was significantly older than the HC group (MDD > HC; $F_{(1, 377)} = 61.51$, $p < 0.001$, $\eta^2 = 0.140$). With regard to the BDI score, a main effect of *Diagnosis* (MDD > HC; $F_{(1, 377)} = 754.98$, $p < 0.001$, $\eta^2 = 0.067$), *Sex* (female > male; $F_{(1, 377)} = 5.47$, $p = 0.020$, $\eta^2 = 0.014$), and a *Diagnosis* × *Sex* interaction effect ($F_{(1,377)} = 5.23$, $p = 0.023$, $\eta^2 = 0.014$) emerged. Simple effects analyses clarified that the female MDD group exhibited a higher BDI score in comparison to the male MDD group ($p_{Bonferroni} = 0.004$). In addition, the female MDD group exhibited a higher HAM-D score than the male MDD group ($t_{(136)} = -2.85$, $p = 0.005$, C*ohen's d* = 0.479). For mean framewise displacement (FD), the female group exhibited a higher mean FD than the male group ($F_{(1, 376)} = 6.61$, $p = 0.011$, $\eta^2 = 0.017$), and no other significant effects were detected (all *p*-values > 0.05).

Co-activation Pattern Characteristics

CAP_1 was mainly characterized by the deactivation of the visual network and sensorimotor network and activation of the anterior cingulate cortex. CAP_2 mainly included the activation of brain regions implicated in the visual network. CAP_3 included the activation of brain regions

involving the visual network, sensorimotor network and dorsal attention network, and deactivation of the anterior cingulate cortex and thalamus. CAP_4 involved the activation of the DMN and deactivation of brain regions overlapping with the SN. CAP_5 was characterized by the activation of brain regions implicated with the sensorimotor network and the deactivation of the visual network. CAP_6 was composed of the activation of brain regions overlapping with the SN and the deactivation of brain regions overlapping with the anterior DMN. CAP_7 was composed of the activation of brain regions overlapping with the DMN and the deactivation of brain regions overlapping with the FPN. CAP_8 was characterized by the activation of brain regions overlapping with the FPN and the deactivation of anterior DMN regions. CAP_9 included the activation of brain regions involving the visual and sensorimotor networks. CAP_{10} is characterized by the activation of the visual and sensorimotor networks.

Pearson correlation analyses to quantify spatial similarity among all CAPs revealed five pairs with opposite spatial distribution (CAP_1/CAP_3, $r = -0.931$, $p < 0.001$; CAP_2/CAP_5, $r = -0.932$, $p < 0.001$; CAP_4/CAP_6, $r = -0.899$, $p < 0.001$; CAP_7/CAP_8, $r = -0.906$, $p < 0.001$; CAP_9/CAP_{10}, $r = -0.975$, $p < 0.001$; *Supplemental Figure S2*). In addition, the mean numbers of transitions between pairs with opposite spatial distribution were the smallest among all CAP pairs ($CAP_1 \rightarrow CAP_3$, 0.315; $CAP_3 \rightarrow CAP_1$, 0.328; $CAP_2 \rightarrow CAP_5$, 0.257; $CAP_5 \rightarrow CAP_2$, 0.318; $CAP_4 \rightarrow CAP_6$, 0.407; $CAP_6 \rightarrow CAP_4$, 0.381; $CAP_7 \rightarrow CAP_8$, 0.192; $CAP_8 \rightarrow CAP_7$, 0.291; $CAP_9 \rightarrow CAP_{10}$, 0.087; $CAP_{10} \rightarrow CAP_9$, 0.089; *Supplemental Figure S2*). The above two patterns were consistent with prior findings [22,23,26,27].

Group Differences in Time Spent in CAP and CAP Persistence in CAP_1, CAP_2, CAP_3, CAP_5, CAP_9 and CAP_{10}

For the "time spent in CAP" metric, *Sex* × *Diagnosis* ANCOVAs revealed a significant *Sex* × *Diagnosis* interaction effect in CAP_2 ($F_{(1,376)} = 8.69$, $p = 0.003$, $p_{FDR} = 0.018$, $\eta^2 = 0.023$; *Supplemental Table S2*). A following Bonferroni-corrected simple effect analysis revealed that the male MDD group spent less time in CAP_2 ($p_{Bonferroni} = 0.028$) in comparison to the male HC group. Additionally, the healthy male group spent more time in CAP_2 in comparison to the healthy female group ($p_{Bonferroni} = 0.027$), whereas the female MDD group spent more time in CAP_2 in comparison to the male MDD group ($p_{Bonferroni} = 0.044$).

For the persistence metric, *Sex* × *Diagnosis* ANCOVAs revealed a significant *Sex* × *Diagnosis* interaction effect in CAP_2 ($F_{(1,376)} = 9.21$, $p = 0.003$, $p_{FDR} = 0.042$, $\eta^2 = 0.019$; *Supplemental Table S3*). A following Bonferroni-corrected simple effect analysis revealed that the male MDD group showed lower persistence in CAP_2 ($p_{Bonferroni} = 0.023$) in comparison to the male HC group. Additionally, the healthy male group showed greater persistence in CAP_2 in comparison to the healthy female group ($p_{Bonferroni} = 0.005$), whereas the female MDD group showed greater persistence in CAP_2 in comparison to the male MDD group ($p_{Bonferroni} = 0.209$).

Group Differences in Static FC within and between SN, DMN and FPN

Diagnosis × *Sex* ANCOVAs revealed a significant main effect of *Diagnosis* ($F_{(1, 376)} = 7.71$, $p = 0.006$, $p_{FDR} = 0.036$, $\eta^2 = 0.020$; *Supplemental Table S8*) in FC within the FPN, with the MDD group exhibiting significantly higher within-FPN FC relative to the HCs. Additionally, a main effect of *Sex* (male > female; $F_{(1,376)} = 9.25$, $p = 0.003$, $p_{FDR} = 0.018$, $\eta^2 = 0.024$; *Supplemental Table S8*) emerged for FC between the SN and FPN, with the males showing higher FC between the SN and FPN compared to the females.

Directly related to the CAP findings, a trend of significant *Diagnosis* × *Sex* interaction effect was observed for FC between the DMN and SN ($F_{(1,373)} = 3.12$, $p = 0.078$, $\eta^2 = 0.008$; *Supplemental Table S8*), which is consistent with the interaction effects observed in time spent and persistence of CAPs exhibiting opposite polarity between the SN and DMN. In addition, a trend of significant main effect of *Diagnosis* was observed in FC between the DMN and FPN (MDD < HC, $F_{(1,376)} = 4.22$, $p = 0.041$, $\eta^2 = 0.011$; *Supplemental Table S8*), which is also in line with the higher persistence of CAP_7 [DMN+FPN-] in individuals with MDD relative to the HCs.

Follow-up Correlation Analyses

Pearson correlation analyses were conducted to test the associations between the CAP metrics that exhibited significant diagnosis-related effects and BDI scores in the male and female MDD groups separately. Time spent in CAP_4 [DMN+SN-] was positively correlated with BDI scores in the male MDD group; however, this association did not survive multiple comparison correction ($r = 0.27$, $p = 0.048$, $p_{FDR} = 0.384$). No other significant correlations emerged (See *Supplemental Table S7* for more details). Results of correlations among all metrics of interests across all subjects were listed in *Supplemental Table S9.*

Supplemental Discussion

Relative to the male HCs, the males with MDD spent more time in two CAPs (DMN+SN-, DMN-SN+) with opposite spatial distribution. Moreover, the time spent in DMN+SN- and DMN-SN+ configurations were highly positively correlated across subjects (see *Supplemental Table S9*). Consistently, a prior study also found significant positive correlation between CAPs exhibiting opposite spatial distributions[28]. Additionally, the time spent in DMN+SN- and SN-DMN+ CAPs were negatively correlated with static FC between the DMN and SN. All these findings reveal that although the DMN+SN- and DMN-SN+ CAPs are spatially anti-correlated, their resting brain dynamics could be associated with similar brain function. Our data suggest that higher BOLD signals in the SN may lower available resources in the DMN, and vice versa. This opposite polarity between the SN and DMN could be the manifestation of a kind of spontaneous resource allocation style, and males with MDD would tend to spend more time in this type of spontaneous resource allocation style relative to sex-matched HCs.

Supplemental Tables

Supplemental Table S1. Descriptive statistics of the ten CAPs.

Characteristics		Min	Max	Skew	Kurt
Occurrence					
	CAP_1	0	59	0.343	− 0.689
	CAP_2	1	62	0.292	− 0.498
	CAP_3	1	67	0.658	− 0.376
	CAP_4	1	73	0.368	− 0.32
	CAP_5	2	51	0.46	− 0.228
	CAP_6	0	67	0.581	− 0.144
	CAP_7	0	59	0.925	0.195
	CAP_8	2	61	0.848	0.454
	CAP_9	1	67	1.411	1.801
	CAP_{10}	0	69	1.242	1.274
Persistence					
	CAP_1	0	43	0.756	− 0.145
	CAP_2	0	42	0.585	− 0.341
	CAP_3	0	48	0.999	0.392
	CAP_4	0	55	0.882	1.109
	CAP_5	0	31	0.741	− 0.104
	CAP_6	0	46	1.201	1.761
	CAP_7	0	43	1.361	1.543
	CAP_8	0	39	1.211	1.585
	CAP_9	0	51	1.901	3.802
	CAP_{10}	0	55	1.817	3.970

Note. Min, minimum; Max, maximum; Skew, skewness of the distribution; Kurt, kurtosis of the distribution.

Supplemental Table S2. Group differences in time spent in CAP_4, CAP_6, CAP_7 and CAP_8.

Characteristics	HC Male (n = 106)	HC Female (n = 137)	MDD Male (n = 55)	MDD Female (n = 83)	*Diagnosis*			*Sex*			*Diagnosis × Sex*		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	p_{FDR}	F	p	p_{FDR}	F	p	p_{FDR}
DMN+SN-	21.90 (10.85)	26.23 (13.86)	26.82 (13.05)	23.19 (11.37)	0.10	0.751	0.751	0.04	0.852	0.852	8.96	0.003	**0.012**
DMN-SN+	18.05 (10.65)	20.72 (12.12)	23.62 (13.36)	20.27 (12.23)	2.55	0.111	0.184	0.10	0.752	0.852	5.54	0.019	**0.038**
DMN+FPN-	19.92 (14.60)	18.03 (10.72)	24.62 (12.06)	20.78 (13.09)	5.20	0.023	0.092	4.59	0.033	0.132	0.55	0.459	0.612
DMN-FPN+	18.55 (11.09)	17.48 (10.18)	20.87 (10.30)	19.12 (11.44)	2.21	0.138	0.184	1.50	0.221	0.442	0.09	0.759	0.759

Note. False discovery rate (FDR) correction was conducted for each effect (i.e., Diagnosis, Sex, Diagnosis × Sex interaction) in the time spent in CAPs of interest. SD, standard deviation; HC, healthy controls; MDD, major depressive disorder; FDR, false discovery rate.

Supplemental Table S3. Group differences in the persistence of CAP_4, CAP_6, CAP_7 and CAP_8.

Characteristics	HC Male (n = 106)	HC Female (n = 137)	MDD Male (n = 55)	MDD Female (n = 83)	*Diagnosis*			*Sex*			*Diagnosis × Sex*		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	p_{FDR}	F	p	p_{FDR}	F	p	p_{FDR}
DMN+SN-	10.62 (7.60)	13.19 (9.70)	13.85 (8.63)	10.94 (7.30)	0.002	0.964	0.964	0.08	0.773	0.773	9.21	0.003	**0.012**
DMN-SN+	2.53 (1.30)	2.68 (1.22)	3.01 (1.53)	2.56 (1.32)	1.07	0.302	0.554	1.22	0.270	0.360	4.38	0.037	0.074
DMN+FPN-	2.65 (1.58)	2.38 (1.18)	3.19 (1.14)	2.72 (1.36)	6.94	0.009	**0.036**	6.77	0.010	**0.040**	0.50	0.479	0.639
DMN-FPN+	2.67 (1.25)	2.44 (1.26)	2.90 (1.16)	2.63 (1.31)	2.05	0.153	0.382	3.46	0.064	0.128	0.02	0.897	0.897

Note. False discovery rate (FDR) correction was conducted for each effect (i.e., Diagnosis, Sex, Diagnosis × Sex interaction) in the persistence of CAPs of interest. SD, standard deviation; HC, healthy controls; MDD, major depressive disorder; FDR, false discovery rate.

Supplemental Table S4. Group differences in the time spent in CAP_4 and CAP_6, the persistence of CAP_4, and the number of transitions from CAP_7 to CAP_4, when controlling for depressive symptoms (BDI scores) and mean framewise displacement.

Characteristics	HC Male (n = 106)	HC Female (n = 137)	MDD Male (n = 55)	MDD Female (n = 83)	*Diagnosis*			*Sex*			*Diagnosis × Sex*		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	p_{FDR}	F	p	p_{FDR}	F	p	p_{FDR}
Time spent in DMN+SN-	21.90 (10.85)	26.23 (13.86)	26.82 (13.05)	23.20 (11.37)	0.61	0.436	0.581	0.48	0.490	0.804	7.22	0.008	**0.016**
Time spent in DMN-SN+	18.05 (10.65)	20.72 (12.12)	23.62 (13.36)	20.27 (12.23)	2.13	0.146	0.562	0.09	0.769	0.804	4.05	0.045	**0.045**
Persistence of DMN+SN-	10.48 (7.48)	13.19 (9.70)	13.85 (8.63)	10.91 (7.34)	0.12	0.726	0.726	0.06	0.804	0.804	7.50	0.006	**0.016**
(*DMN+FPN-*)→(DMN+SN-)	1.06 (0.77)	1.19 (0.81)	1.45 (0.94)	1.17 (0.82)	1.17	0.281	0.562	0.21	0.650	0.804	4.61	0.033	**0.044**

Note. False discovery rate (FDR) correction was conducted for each effect (i.e., Diagnosis, Sex, Diagnosis × Sex interaction) regarding the metric of interest. MDD, major depressive disorder; HC, healthy controls; SD, standard deviation; BDI, Beck Depression Inventory; FDR, false discovery rate.

Supplemental Table S5. Group differences on CAP metrics for CAP_1, CAP_2, CAP_3, CAP_5, CAP_9, and CAP_{10}.

	HC Male (n = 106)	HC Female (n = 137)	MDD Male (n = 55)	MDD Female (n = 83)	*Diagnosis*			*Sex*			*Diagnosis × Sex*		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	p_{FDR}	F	p	p_{FDR}	F	p	p_{FDR}
Time Spent													
CAP_1	26.70 (13.46)	25.66 (13.49)	25.16 (12.92)	25.02 (13.09)	0.49	0.484	0.726	0.17	0.683	0.917	0.10	0.756	0.756
CAP_2	27.58 (12.34)	24.16 (11.35)	23.21 (12.46)	27.48 (12.05)	0.23	0.635	0.762	0.09	0.764	0.917	8.69	0.003	**0.018**
CAP_3	24.45 (13.04)	26.36 (15.29)	24.93 (12.82)	22.83 (13.28)	0.87	0.351	0.702	0.004	0.950	0.950	1.75	0.187	0.224
CAP_5	22.27 (9.34)	20.72 (10.45)	19.07 (8.79)	22.31 (9.24)	0.08	0.776	0.776	0.81	0.369	0.738	5.50	0.020	0.060
CAP_9	3.71 (1.55)	3.74 (1.47)	3.21 (1.21)	3.74 (1.32)	1.73	0.190	0.570	3.34	0.068	0.408	2.75	0.098	0.147
CAP_{10}	3.75 (1.54)	3.63 (1.52)	3.11 (1.30)	3.62 (1.50)	1.75	0.186	0.570	1.71	0.192	0.576	4.15	0.042	0.084
Persistence													
CAP_1	14.31 (10.42)	13.01 (10.05)	12.95 (10.15)	12.64 (10.43)	0.49	0.487	0.487	0.51	0.475	0.810	0.20	0.652	0.652
CAP_2	14.51 (9.31)	11.33 (7.85)	11.27 (9.31)	13.23 (8.68)	0.66	0.417	0.487	0.47	0.495	0.910	7.33	0.007	**0.042**
CAP_3	12.42 (9.51)	13.91 (11.47)	12.87 (9.85)	10.96 (9.87)	1.02	0.314	0.487	0.03	0.859	0.943	2.27	0.132	0.158
CAP_5	10.48 (6.40)	8.83 (6.64)	8.10 (5.82)	9.57 (6.65)	0.75	0.389	0.487	0.005	0.943	0.943	5.09	0.025	0.075
CAP_9	2.28 (1.61)	2.19 (1.62)	1.68 (1.23)	2.17 (1.48)	2.38	0.124	0.372	1.50	0.222	0.810	2.88	0.091	0.136
CAP_{10}	2.38 (1.58)	2.14 (1.57)	1.63 (1.27)	2.05 (1.59)	3.51	0.062	0.372	0.38	0.540	0.810	4.13	0.043	0.086

Note. False discovery rate (FDR) correction was conducted for each effect (i.e., Diagnosis, Sex, Diagnosis × Sex interaction) regarding the metric of interest. SD, standard deviation; HC, healthy controls; MDD, major depressive disorder; FDR, false discovery rate.

Supplemental Table S6. Group differences on the number of transitions between CAP_4, CAP_6 and CAP_7.

Characteristics	HC Male (n = 106)	HC Female (n = 137)	MDD Male (n = 55)	MDD Female (n = 83)	*Diagnosis*			*Sex*			*Diagnosis × Sex*		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	p_{FDR}	F	p	p_{FDR}	F	p	p_{FDR}
CAP_4 to CAP_7	1.21 (0.88)	1.32 (0.83)	1.54 (0.89)	1.28 (0.84)	1.07	0.303	0.404	0.84	0.359	0.724	4.02	0.046	0.061
CAP_7 to CAP_4	1.06 (0.77)	1.19 (0.88)	1.45 (0.94)	1.17 (0.82)	1.48	0.224	0.404	0.83	0.362	0.724	5.58	0.017	**0.044**
CAP_6 to CAP_7	0.53 (0.66)	0.68 (0.78)	0.81 (0.85)	0.61 (0.69)	0.27	0.607	0.607	0.15	0.696	0.924	5.27	0.022	**0.044**
CAP_7 to CAP_6	0.56 (0.65)	0.65 (0.74)	0.88 (0.86)	0.80 (0.82)	6.14	0.014	0.056	0.01	0.924	0.924	1.18	0.279	0.279

Note. False discovery rate (FDR) correction was conducted for each effect (i.e., Diagnosis, Sex, Diagnosis × Sex interaction) in the transitions among CAPs exhibiting significant group differences. CAP_4, DMN+SN-; CAP_6, DMN-SN+; CAP_7, DMN+FPN-; CAP_8, DMN-FPN+. SD, standard deviation; HC, healthy controls; MDD, major depressive disorder; FDR, false discovery rate.

Supplemental Table S7. Correlation analyses.

Characteristics	BDI		
	r	*p*	p_{FDR}
MDD female			
Time spent in DMN+SN-	− 0.15	0.177	0.708
Time spent in DMN-SN+	− 0.09	0.446	0.892
DMN+FPN- Persistence	− 0.004	0.976	0.993
(DMN+FPN-) → (DMN+SN-)	− 0.01	0.954	0.993
MDD male			
Time spent in DMN+SN-	0.27	0.048	0.384
Time spent in DMN-SN+	0.04	0.792	0.993
DMN+FPN- Persistence	− 0.001	0.993	0.993
(DMN+FPN-) → (DMN+SN-)	0.13	0.328	0.875

Note. MDD, major depressive disorder; BDI, Beck Depression Inventory-II; FDR, false discovery rate.

Supplemental Table S8. Group difference in static FC within and between the SN, DMN and FPN.

Characteristics	HC Male (n = 106)	HC Female (n = 137)	MDD Male (n = 55)	MDD Female (n = 83)	*Diagnosis*			*Sex*			*Diagnosis × Sex*		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F	p	p_{FDR}	F	p	p_{FDR}	F	p	p_{FDR}
Mean DMN FC	0.298 (0.097)	0.292 (0.101)	0.303 (0.113)	0.272 (0.112)	1.061	0.304	0.346	2.907	0.089	0.178	1.276	0.259	0.518
Mean SN FC	0.361 (0.120)	0.355 (0.101)	0.348 (0.095)	0.322 (0.099)	2.834	0.093	0.162	1.852	0.174	0.261	0.675	0.412	0.618
Mean FPN FC	0.290 (0.093)	0.279 (0.097)	0.264 (0.084)	0.254 (0.100)	7.708	0.006	**0.036**	1.147	0.285	0.342	<0.001	0.998	0.998
Mean DMN-FPN FC	0.129 (0.087)	0.108(0.084)	0.105(0.088)	0.092(0.092)	4.216	0.041	0.123	3.244	0.072	0.178	0.153	0.696	0.838
Mean DMN-SN FC	−0.063(0.106)	−0.087(0.091)	−0.099 (0.109)	−0.085 (0.089)	2.601	0.108	0.162	0.239	0.625	0.625	3.115	0.078	0.408
Mean SN-FPN FC	0.042(0.091)	0.028(0.089)	0.048(0.081)	0.008(0.066)	0.890	0.346	0.346	9.247	0.003	**0.018**	2.233	0.136	0.408

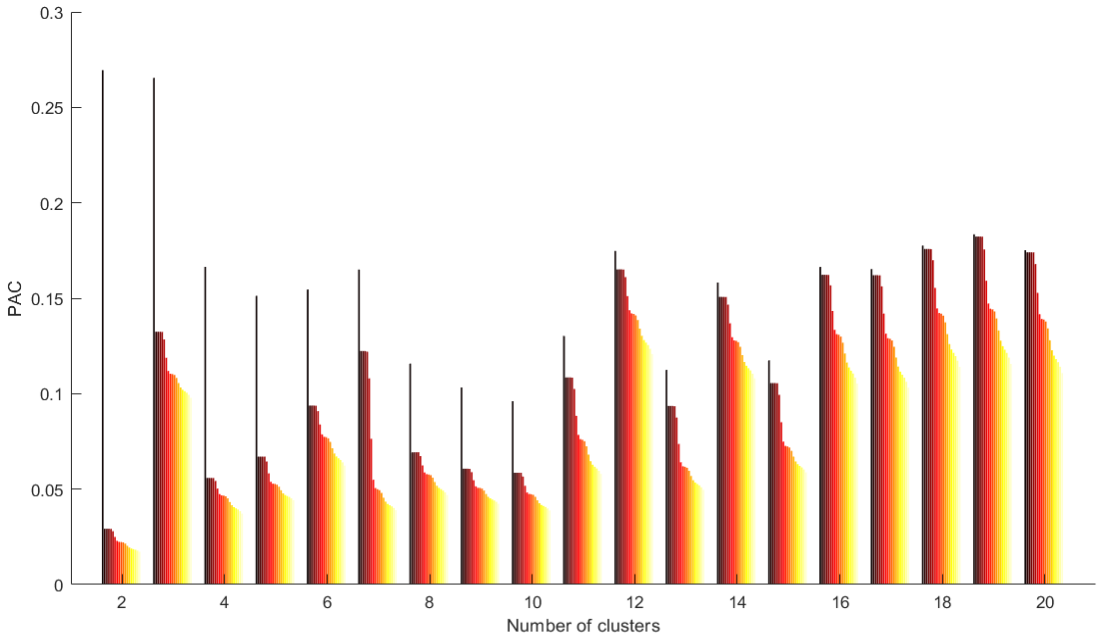
Note. False discovery rate (FDR) correction was conducted for each effect (i.e., Diagnosis, Sex, Diagnosis × Sex interaction) regarding the static-FC within and between the SN, DMN and FPN. SD, standard deviation; HC, healthy controls; MDD, major depressive disorder; FDR, false discovery rate; DMN, default mode network; SN, salience network; FPN, frontoparietal network.

Supplemental Table S9. Correlations among all metrics of interest.

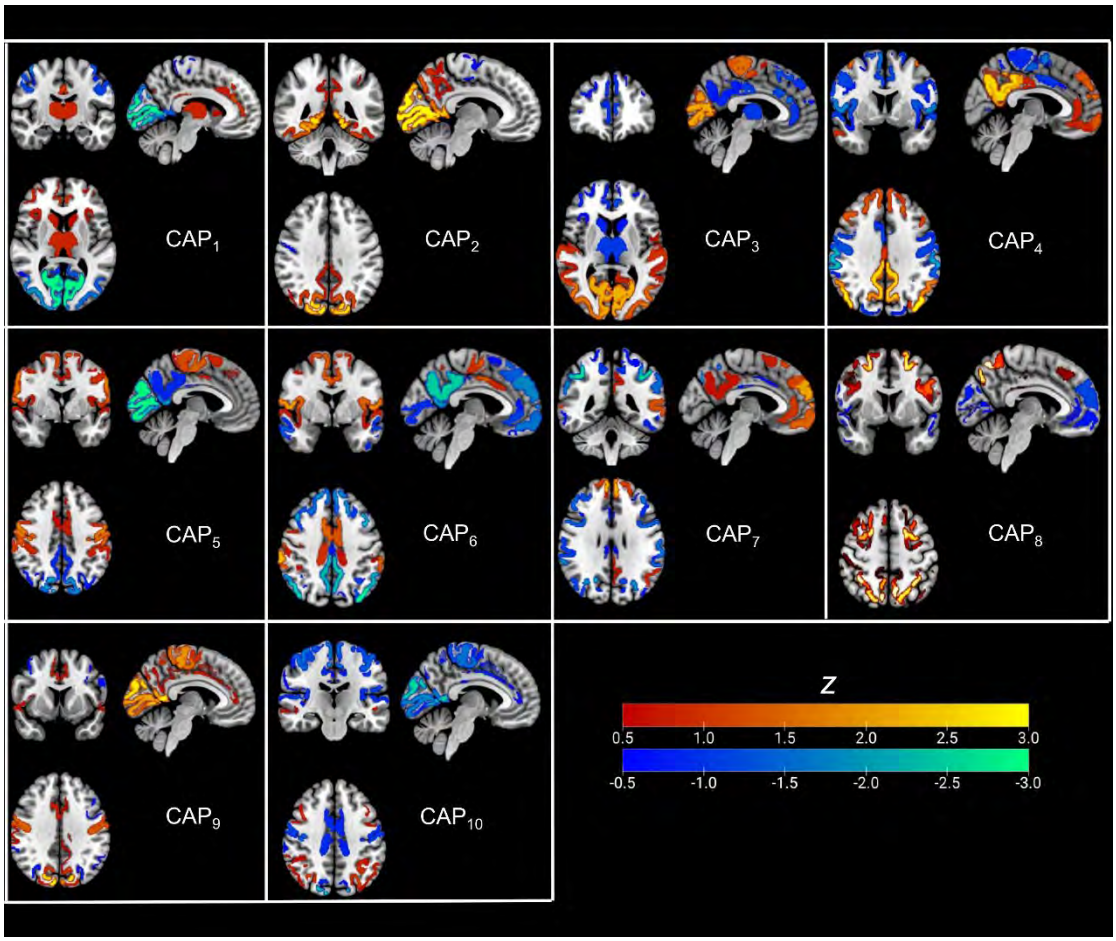
		Time Spent				Persistence				Static FC					
		DMN+SN-	*DMN-SN+*	*DMN+FPN-*	*DMN-FPN+*	DMN+SN-	DMN-SN+	DMN+FPN-	DMN-FPN+	DMN	SN	FPN	DMN-FPN	SN-DMN	SN-FPN
Time Spent	*DMN+SN-*	-	0.79***	0.42***	0.36***	0.95***	0.72***	0.34***	0.28***	0.15**	0.23***	0.04	-0.16**	-0.54***	-0.28***
	DMN-SN+	-	-	0.63***	0.52***	0.73***	0.95***	0.57***	0.46***	0.21***	0.33***	-0.02	-0.24***	-0.57***	-0.27***
	DMN+FPN-	-	-	-	0.79***	0.34***	0.58***	0.96***	0.73***	0.04	0.11*	0.05	-0.36***	-0.39***	-0.08
	DMN-FPN+	-	-	-	-	0.27**	0.46***	0.76***	0.95***	-0.06	0.02	0.12*	-0.29***	-0.26***	-0.12*
Persistence	*DMN+SN-*	-	-	-	-	-	0.70***	0.27***	0.22***	0.19***	0.25***	0.05	-0.11*	-0.57***	-0.25***
	DMN-SN+	-	-	-	-	-	-	0.53***	0.43***	0.26***	0.37***	0.003	-0.19***	-0.57***	-0.25***
	DMN+FPN-	-	-	-	-	-	-	-	0.72***	0.03	0.10*	0.05	-0.34***	-0.35***	-0.07
	DMN-FPN+	-	-	-	-	-	-	-	-	-0.05	0.02	0.14**	-0.26***	-0.24***	-0.10*
Static FC	DMN	-	-	-	-	-	-	-	-	-	0.26***	0.32***	0.58***	0.10	0.13**
	SN	-	-	-	-	-	-	-	-	-	-	0.18***	0.14**	0.06	0.40***
	FPN	-	-	-	-	-	-	-	-	-	-	-	0.51***	0.22***	0.18***
	DMN-FPN	-	-	-	-	-	-	-	-	-	-	-	-	0.54***	0.22***
	SN-DMN	-	-	-	-	-	-	-	-	-	-	-	-	-	0.60***
	SN-FPN	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. DMN, default mode network; SN, salience network; FPN, frontoparietal network. $^{*}p < 0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

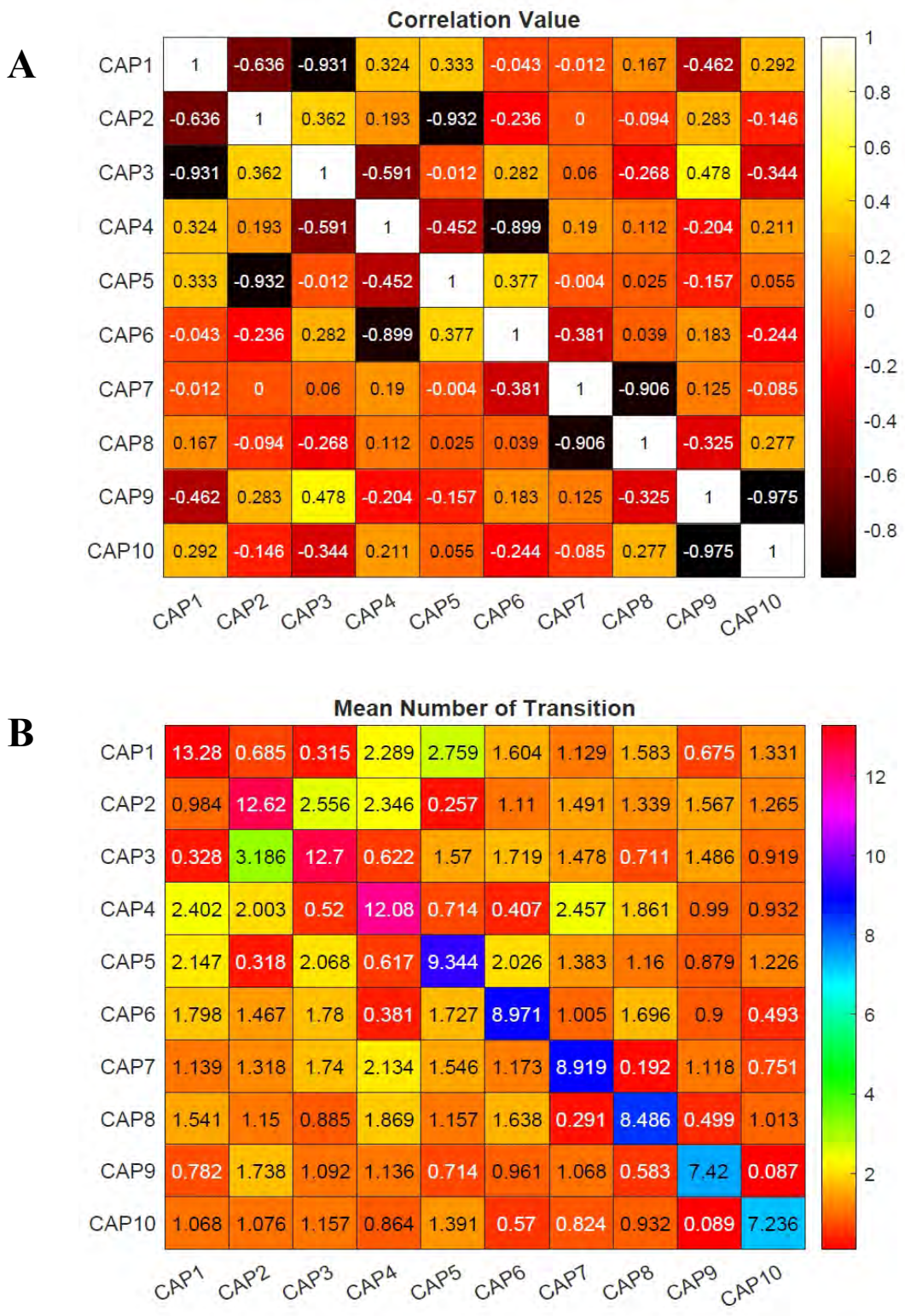
Supplemental Figures



Supplemental Figure S1. Consensus clustering yields $K = 10$ as an optimal number of clusters. The y-axis indicates the percentage of ambiguously clustered frames (PAC) across candidate cluster numbers. A lower PAC values denotes a higher clustering quality. The color gradient for a given cluster number denotes the assessment of PAC with a more or less strict definition of "ambiguous clustering" (darker shades denote a stricter one).



Supplemental Figure S2. Ten co-activation patterns (CAPs). Each CAP was characterized by the activation and deactivation of brain regions. Warm colors indicate activation and cold colors denote deactivation. Z-scored CAPs are displayed at $0.5 \leq |Z| \leq 3.0$. The ten CAPs included: 1) CAP_1 involving activations of the anterior cingulate cortex and thalamus, and deactivations of visual network regions; 2) CAP_2 involving activations of visual network regions; 3) CAP_3 involving activations of visual, sensorimotor, and dorsal attention network regions and deactivations of the anterior cingulate cortex and thalamus; 4) CAP_4 involving activations of DMN regions and deactivations of salience network regions; 5) CAP_5 involving activations of sensorimotor network regions and deactivations of visual network regions; 6) CAP_6 involving activations of salience network regions and deactivations of DMN regions; 7) CAP_7 involving activations of DMN regions and deactivations of FPN regions; 8) CAP_8 involving activations of FPN regions and deactivations of anterior DMN regions; 9) CAP_9 involving activations of visual and sensorimotor network regions; 10) CAP_{10} involving deactivations of visual and sensorimotor network regions.



Supplemental Figure S3. Spatial similarity between CAPs and transition probabilities across CAPs. (**A**) Spatial similarity among the 10 CAPs. CAP_1 exhibited largely negative correlation with CAP_3, CAP_2 with CAP_5, CAP_4 with CAP_6, CAP_7 with CAP_8, and CAP_9 with CAP_{10}. (**B**) Mean number of transitions across the 10 CAPs. The mean number of transitions between CAPs exhibiting opposite spatial patterns is the smallest for each CAP.

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