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Original Article

Role of the amygdala in disrupted integration and effective connectivity of cortico-subcortical networks in apathy

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Background: Apathy is a quantitative reduction in motivation and goal-directed behaviors, not only observed in neuropsychiatric disorders, but also present in healthy populations. Although brain abnormalities associated with apathy in clinical disorders have been studied, the organization of brain networks in healthy individuals has yet to be identified.
Method: We examined properties of intrinsic brain networks in healthy individuals with varied levels of apathy. By using functional magnetic resonance imaging in combination with graph theory analysis and dynamic causal modeling analysis, we tested communications among nodes and modules as well as effective connectivity among brain networks.
Results: We found that the average participation coefficient of the subcortical network, especially the amygdala, was lower in individuals with high than low apathy. Importantly, we observed weaker effective connectivity fromthe hippocampus and parahippocampal gyrus to the amygdala, and from the amygdala to the parahippocampal gyrus and medial frontal cortex in individuals with apathy.
Conclusion: These findings suggest that individuals with high apathy exhibit aberrant communication within the cortical-to-subcortical network, characterized by differences in amygdala-related effective connectivity. Our work sheds light on the neural basis of apathy in subclinical populations and may have implications for understanding the development of clinical conditions that feature apathy.

Key words: amygdala; cortico-subcortical network; graph theory; dynamic causal modeling.

Introduction

Apathy has been described as a loss of motivation and characterized by decreases in the behavioral, cognitive, and emotional concomitants of goal-directed behavior (Marin et al. 1991; Levy and Czernecki 2006). It is a clinical feature of many neuropsychiatric conditions (den Brok et al. 2015; Yuen et al. 2015; Ruthirakuhan et al. 2018; Servaas et al. 2019; Xu et al. 2019), which has been reported in 55% patients with Alzheimer's disease (Robert et al. 2009) and 39.4% in Parkinson's disease (den Brok et al. 2015). Besides, apathy is also recognized to a certain degree in healthy individuals (Bonnelle et al. 2015; Klaasen et al. 2017; Kos et al. 2017) and significantly influences the quality of life (Pardini et al. 2016). As yet, the position of apathy in current nosology remains poorly defined. Studies focused on subclinical individuals could find useful biomarker in the prediction of progression to more severe apathetic conditions and contribute to refine current concepts of apathy as an independent clinical syndrome

Levy and Dubois proposed three subtypes of apathy, characterized by either emotional-affective, cognitive, or auto-activation deficits. That is, the quantitative reduction of voluntary and purposeful behaviors that constitute apathy may be due to (i) the inability to engage emotional processes necessary for motivation, (ii) the impairment of the cognitive functions needed to elaborate action plans, or (iii) difficulties in self-initiating thoughts or actions (Levy and Dubois 2006). Brain networks underlying these functions have been hypothesized to be relevant for apathy in clinical as well as nonclinical populations (Klaasen et al. 2017; Saleh et al. 2021).

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Neural mechanisms underlying the apathetic syndrome have been uncovered in clinical disorders, suggesting that apathy is associated with abnormal functioning of frontal-basal ganglia circuits (Levy and Czernecki 2006; Kos et al. 2017; le Heron et al. 2019). To date, however, only a few of studies have directly examined brain architecture of subclinical apathy in healthy individuals. Some studies have shown associations of apathy with abnormal prefrontal activity and its defective connectivity with basal ganglia during cognitive performance (Fazio et al. 2016; Klaasen et al. 2017), whereas others did not (Kos et al. 2017), which may depend on the specific cognitive task used. Structural changes in the medial frontal cortex (MFC), anterior cingulate cortex (ACC) and thalamus have been associated with higher apathy in the healthy population (Spalletta et al. 2013; Bonnelle et al. 2015). These findings link apathy to alterations of specific brain regions in healthy individuals with.

The human brain is a large-scale complex network, simultaneously segregated and integrated via specific connectivity patterns (Bullmore and Sporns 2009). Normal functions are not only driven by activity of local brain regions but also by the communications among global brain networks (Pessoa 2014; Grayson et al. 2016; Sporns and Betzel 2016; Bassett and Sporns 2017). Graph theory has been used in several studies, which have shown task independent as well as task-specific network property alterations (Rubinov and Sporns 2010; Wang et al. 2020). Regarding apathy, previous studies have shown reduced local efficiency of the ACC (Onoda and Yamaguchi 2015) but increased communication efficiency in prefrontal and limbic reward areas (Ely et al. 2021). These findings make it possible to identify the network properties of apathy in healthy populations. Resting-state brain activity reflects intrinsic brain fluctuations, and its intrinsic network architecture represents a standard state of brain organization that responds to task demands as necessary (Cole et al. 2014; Bolt et al. 2017). Therefore, examining brain network properties at rest by using graph-theoretical approaches can help to identify a universal intrinsic network architecture associated with apathy, which will provide additional insights into its neural mechanism.

In this study, we aimed to examine intrinsic organizations of brain networks in healthy individuals with varied levels of apathy. We used participation coefficient (PC), an indicator of graph theory-based analysis, to explore how nodes communicate between modules in brain networks (Guimera and Amaral 2005; Rubinov and Sporns 2010). Next, we examined the effective connectivity between the specific networks by using dynamic causal modeling (DCM) (Friston et al. 2014, 2016). DCM analysis is dependent on a model of interactions or coupling to estimate directional relationship among brain regions (Friston et al. 2014). We hypothesized that altered communications between cortical and subcortical networks would be observed in individuals with high apathy.

Materials and methods

Participants

A total of 204 undergraduate students took part in the experiment. All participants were right-handedness, normal or corrected to normal vision, magnetic resonance imaging-compatibility, and no history of neurological and psychiatric disorders or head injury. Participants were divided into two groups based on the levels of apathy measured by Apathy Evaluation Scale (AES), whose scores were in the top 25% (≥26) were classified as high apathy group and those whose scores were in the bottom 25% (≤16) were classified as low apathy group. According to AES evaluation criteria, those with scores greater than 27 were considered as apathetic in clinical (Faerden et al. 2009; Servaas et al. 2019). Here, the lowest point was 26 for high apathy group, of them 43 of 204 (21%) participants in our sample reached the level of apathy, which is consistent with previous studies (Gillan and Daw 2016; Patzelt et al. 2018; Petitet et al. 2021). Three participants were excluded because of excessive head motion (exceeding 2.5 mm maximum translation, 2.5 degree rotation or 0.2-mm mean frame-wise displacement. The final sample consisted of 50 participants in the high apathy group (20 females; age = 19.46 ±1.62) and 49 participants in the low apathy group (27 females; age = 19.55± 1.47). The study was approved by the local Ethics Committee at Shenzhen University and written informed consent was obtained from each participant.

Apathy assessment

To assess apathy, we used the self-rated version of the AES (Marin et al. 1991; Lueken et al. 2007; Faerden et al. 2008). It is a frequently utilized scale for assessing and quantifying the affective behavioral and cognitive domains of apathy. It has been proved to have a good validity and reliability, useful in discriminating apathy from standard measure of depression and anxiety (Lueken et al. 2007; Clarke et al. 2011). This inventory consists of 18 items, each answer being scored on a 4-point Likert scale from 1 (not at all) to 4 (severely). Higher AES scores indicate more severe apathy. Given the association of apathy with depression (Starkstein et al. 2005), we measured depression by using Beck Depression Inventory (BDI) (Beck et al. 1961) and anhedonia by using the Snaith–Hamilton pleasure scale (SHAPS) (Snaith et al. 1995).

Image acquisition

Magnetic resonance imaging (MRI) data were acquired with a Siemens Prisma 3T scanner at Shenzhen University. Both the functional magnetic resonance imaging (fMRI) and high-resolution 3D structural brain data were obtained using a 64-channel phased array head coil. Head movement was restricted by foam pads fixating the head and scanner noise was reduced by wearing earplugs. Resting state MRI data were acquired by measuring the blood oxygen level dependent (BOLD) signal with a gradient-echo echo planer imaging (EPI)

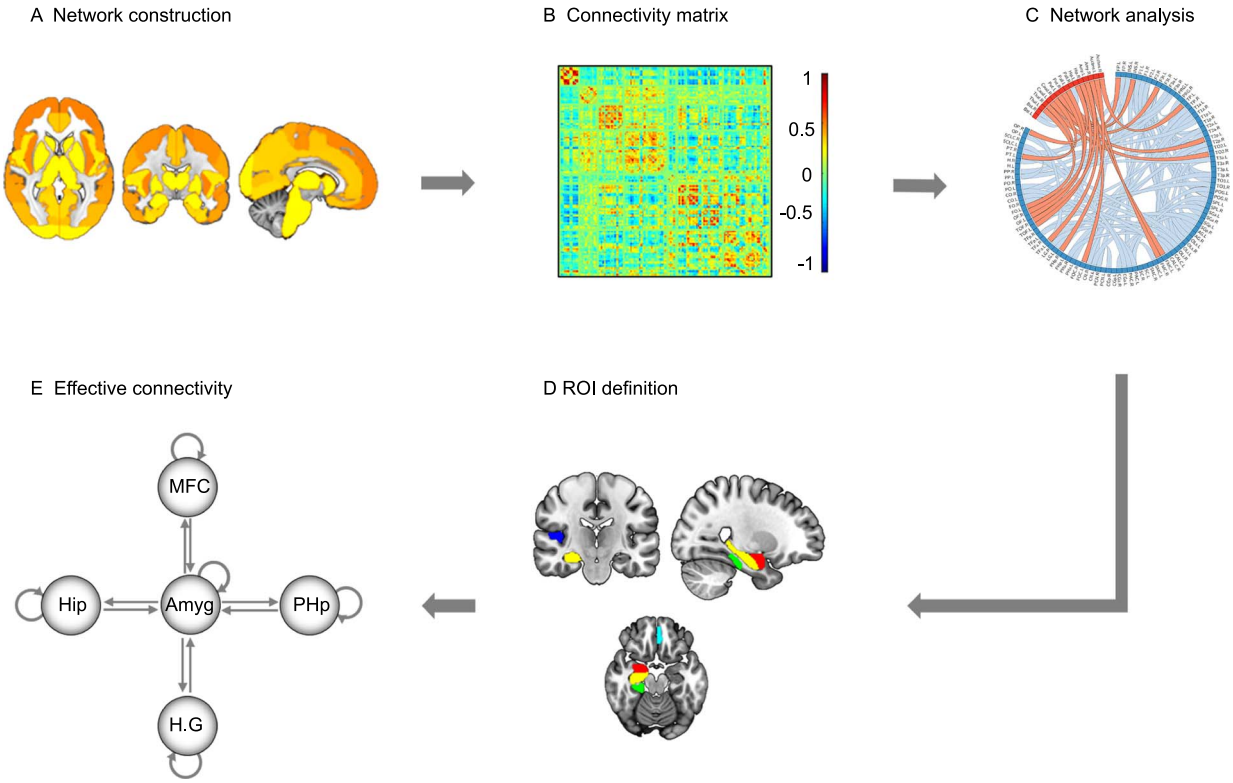

Fig. 1. Analytical pipeline of resting-state fMRI data processing for examination of network property and effective connectivity. Data processing can be subdivided into five main steps: (A) network construction, (B) connectivity matrix, (C) network analysis, (D) ROI definition and (E) effective connectivity. ROI, region of interest; PC, participant coefficient; VOI, volume of interest; DCM, dynamic causal modeling; PEB, parametric empirical Bayes; BMA, Bayesian model averaging.

sequence with the following parameters: repetition time (TR) = 1,000 ms, echo time (TE) = 30 ms, slice thickness 2 mm with gap 2 mm, 65 multi-band slices, flip angle = 90 degrees, field of view (FOV) = 232 × 256 mm, data matrix = 96 × 96, 720 volumes scanned in 12 minutes. The 3D structural brain images were acquired for each participant using a T1-weighted 3D magnetization prepared rapid gradient echo sequence with the following parameters: TR/TE = 2300 ms/2.26 ms, flip angle = 8 degrees, data matrix = 232 × 256, FOV = 232 × 256 mm, bandwidth = 200 Hz/pixel, 192 image slices along the sagittal orientation, obtained in about 7 minutes. During resting-state scanning, all participants were instructed to keep still, open their eyes, gaze at the fixation point on the screen, and think of nothing in particular. No participant reported to be asleep during the scan.

Preprocessing

fMRI data were preprocessed with DPABI (http://rfmri.org/dpabi); a software package based on SPM12 (version no.7219; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). It comprised the following steps: (i) removing the first 10 volumes to decrease the signal's instability; (ii) slice timing; (iii) realignment; (iv) co-registering the T1-weighted image to the corresponding mean functional image; (v) segment; (vi) regressing out head motion parameters, including autoregressive models of motion incorporating 6 head motion parameters, 6 head motion parameters one time point before and 12 corresponding squared items (Buchel et al. 1996; Yan et al. 2013). We used a component-based noise reduction method (CompCor) to correct for physiological noise by regressing out the first five principal components consisting of white matter (WM) signal and cerebrospinal fluid (CS) signal (Behzadi et al. 2007); (vii) detrending; (viii) normalizing to standard Montreal Neurological Institute space (MNI template) and resampled to a voxel size of $2 \times 2 \times 2$ mm^3; (ix) smoothing with a Gaussian kernel of 4 mm full width at half maximum (FWHM); and (x) filtering (0.01–0.1 Hz).

Functional network construction

To define the circuit a priori, we applied the Harvard–Oxford atlas, which distributed brain regions into 112 anatomical regions including 96 cortical and 16 subcortical regions (Fig. 1a). Then, we extracted the time courses of 112 regions of interest (ROIs) from each participant and computed Pearson correlations (via Fisher's z transformation) of all time course pairs to obtain ROI-to-ROI functional connectivity matrix (Fig. 1b). To construct a comparable graph network, a proportional threshold (10%) was used to ensure the same number of network edges for each participant in the present study. This threshold is capable of maintaining a balance between the use of very sparse graphs and denser graphs (Latora and Marchiori 2001; Reineberg and Banich 2016).

Graph theory analysis

To examine interactions among cortical and subcortical brain networks, we used graph theory, a framework describing brain modular organizations based on relationships between nodes and edges (Bullmore and Sporns 2009; Rubinov and Sporns 2010; Wang et al. 2011). All graphical measures were calculated using GRETNA (https://www.nitrc.org/projects/gretna). We first calculated the PC to quantify the degree of network integration (Fig. 1c). A PC_i measures the proportion of inter- and intra-module connections for a specific node, calculated as below,

$$PC_i = 1 - \sum_{m \in M} \left(\frac{k_{im}}{k_i} \right)^2 \quad (1)$$

where m refers to a module in a set of modules M, k_{im} refers to the number of connections between node i and module m, and k_i is the total number of connections of node i in the whole brain network (Guimera and Amaral 2005). Generally, PC will be close to zero if one node is highly integrated with other nodes in its own module but less integrated with nodes in other modules; inversely, PC will be close to one if the node is less integrated with the nodes in its own module but is highly integrated with nodes in other modules. Here, we used the average PC of cortical network and subcortical network to characterize network integration (network level). We calculated each PC of 16 subcortical regions (node level) based on the results of network level.

In addition to PC, we also calculated the number of connections within each network, and the number of connections between cortical and subcortical networks. These measures can provide insights into information communications within and between networks.

Dynamic causal modeling analysis

To examine effective connectivity between cortical and subcortical networks, we implemented DCM analysis by DCM12.5 (revision 7487) based on SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). As described in previous studies (Friston et al. 2003; Zeidman et al. 2019a, 2019b), We constructed a general linear model (GLM) at individual level and extracted the time series from the specific ROI based on the PC results at the node level. That is, nodes showing a significant group difference in PC values were defined as ROIs for DCM analysis (Fig. 1d). A "full" model was then specified for each participant.

After the model estimation, the parametric empirical Bayes (PEB) method was applied to quantify the group effect. It conveys both the estimated connection strengths and their uncertainty (i.e. posterior covariance) from the participant to the group level (Zeidman et al. 2019b). Here, we identified two centered variables for design matrix specification of the PEB model: (i) the mean of the whole sample; (ii) the group difference between high apathy and low apathy. Exploratory and estimation Bayesian model reduction was subsequently applied to optimize the fully connected model. Then, we performed an automatic search over reduced PEB models and calculated a Bayesian model average (BMA) to determine the connection parameters that best explained effective connectivity of the group difference. The threshold was set as a posterior probability (P_p) > 0.95.

Statistical analyses

One-way ANCOVA were conducted with SPSS 20.0 to test the group differences (high apathy vs. low apathy) on the average PC of the two functional networks, controlling for BDI and SHAPS scores. One-sample and two-sample t tests were performed on the functional connectivity matrix to describe patterns contributing to network integration. Chi-square was used to test the gender difference. Bonferroni correction was used to control for multiple comparisons. At the network level, the significant threshold was set at $\alpha = 0.05/2$ (two networks) $= 0.025$. At the node level, the significant threshold was set at $\alpha = 0.05/n$ (n subcortical regions).

Results

Demographic characteristics

There was no difference in gender, age or education between high and low apathy group (Table 1). The AES scores of high apathy group was significantly higher than those of low apathy group, $t = 25.91$, $P < 0.001$. BDI ($t = 4.98$, $P < 0.001$) and SHAPS ($t = 7.07$, $P < 0.001$) scores were also significantly higher in high apathy group than in low apathy group, respectively.

Graph theoretical analyses

Participation coefficient differences on networks

The ANCOVA analysis was conducted for PC values on each network. The dependent variable was the PC value of networks, the independent variable was the apathy group, and the covariates were the BDI scores and SHAPS scores. The check of the precondition of ANCOVA showed the interaction items between BDI score and group, SHAPS score and group were not significant (BDI × group: $F_{(1,99)} = 1.57$, $P = 0.098$, $\eta^2 = 0.582$; SHAPS × group: $F_{(1,99)} = 1.59$, $P = 0.095$, $\eta^2 = 0.576$), thus qualifying for the precondition of covariate regression consistency. Subsequently, the ANCOVA analysis showed that the average PC value of the subcortical network was significantly lower in high apathy group than in low apathy group, $F_{(1,99)} = 5.456$, $P = 0.022$, $\eta^2 = 0.054$. No significant group difference in cortical network was observed, $F_{(1,99)} = 0.025$, $P = 0.875$, $\eta^2 < 0.001$. Analyses on intra-module and inter-module connections of the cortical and subcortical networks showed that compared to the low apathy group, the high apathy group exhibited decreased intra-module connections in the subcortical network, $F_{(1,99)} = 4.352$, $P = 0.040$, $\eta^2 = 0.044$; there was no significance different between groups for intra-module connections in the cortical network ($F_{(1,99)} = 3.836$, $P = 0.053$, $\eta^2 = 0.039$) nor for inter-module connections between the two networks ($F_{(1,99)} = 3.229$,

Table 1. Demographic information and PC results.

	Low apathy (M ± SD)	High apathy (M ± SD)	χ^2/t/F	P
	$n = 49$	$n = 50$		
$Gender_{(F/M)}$	27/22	20/30	2.91	0.09
Age	19.55 (1.62)	19.46 (1.47)	0.29	0.77
Education	14.14 (1.55)	14.06 (1.38)	0.28	0.78
BDI	3.86 (4.12)	10.30 (8.08)	−4.98	<0.001
SHAPS	19.33 (4.50)	26.50 (5.08)	−7.07	<0.001
AES	14.73 (1.37)	30.32 (3.99)	−25.91	<0.001
$PC_{cortical}$	0.26 (0.43)	0.26 (0.54)	0.03	0.875
$P_{subcortical}$	0.42 (0.12)	0.35 (0.13)	5.46	0.022
$Connection_{cortical}$	492 (28.46)	508 (34.39)	3.84	0.053
$Connection_{subcortical}$	13 (5.69)	10 (5.79)	4.35	0.044
$Connection_{between}$	116 (24.96)	104 (30.24)	3.23	0.076

Note: M, mean value; SD, standard deviation; F/M, female/male; BDI, Beck Depression Inventory; SHAPS, Snaith–Hamilton pleasure scale; AES, Apathy Evaluation Scale; PC, participation coefficient.

$P = 0.076$, $\eta^2 = 0.033$; Fig. 2, Table 1). Analyses with or without global signal regression showed similar results (see Supplemental Table S1).

Participation coefficient and functional connectivity on region of interests

We further compared PC values of 16 ROIs of the subcortical network between two groups. We found high apathy group exhibited significantly decreased PC in the right amygdala, $t = -3.29$, $p_{corrected} = 0.001$. The two-sample t test of ROI-to-ROI functional connectivity showed that functional connectivity of the right amygdala with the right hippocampus ($t = -4.17$, $p_{corrected} < 0.001$), right parahippocampal gyrus ($t = -2.09$, $p_{uncorrected} = 0.039$), right Heschl's gyrus ($t = 2.21$, $p_{uncorrected} = 0.029$) and the left MFC ($t = -2.19$, $p_{uncorrected} = 0.030$) were significantly lower in the high apathy group than in the low apathy group (Fig. 3).

Dynamic causal modeling results

DCM analyses showed that compared to low apathy group, the high apathy group exhibited less inhibition within the parahippocampal gyrus (connectivity strength = −0.23, $P_p = 0.95$; Fig. 4). Compared to the low apathy group, the high apathy group exhibited significantly enhanced excitatory connectivity from the hippocampus to the amygdala (connectivity strength = 0.22, $P_p = 0.95$), increased inhibition from the parahippocampal gyrus to the amygdala (connectivity strength = −0.14, $P_p = 0.95$), increased inhibition from the amygdala to the parahippocampal gyrus (connectivity strength = −0.23, $P_p = 0.95$) and to the MFC (connectivity strength = −0.24, $P_p = 0.95$).

Correlations between apathy level and network properties

We calculated the Pearson's correlations among AES scores, BDI scores, SHAPS scores and network properties including PC, intra-module and inter-module connections in each group. There was no significant correlation among them (Ps > 0.05).

Discussion

In this study, we examined properties of intrinsic brain networks in individuals with varying levels of apathy by using graph theory and DCM analyses. We show large-scale alterations of communications between cortical and subcortical networks, especially the amygdala-centered networks, in apathetic individuals. These results map alterations of the global brain network organization in susceptibility to apathy.

Defective integration of cortical and subcortical networks

We observed significant decreases of PC values of subcortical network in the high apathy group, indicating that brain regions of the subcortical network were highly integrated with others within the subcortical network but communicate less with nodes in the cortical network. Combined with decreased intra-module connections in the subcortical network, these findings suggest reduced levels of internal and external information transfer affecting the subcortical network in individuals with high apathy. It has been proposed that information processing within a network is necessary for effective implementation of specific cognitive processes whereas the exchange of information between more widespread networks is responsible for the coordination and integration of divergent cognitive processes (Rubinov and Sporns 2010; Wang et al. 2011; Zhang et al. 2011). Moreover, a recent task-dependent study also showed that PC and module connections were strongly correlated with executive control during a dot-response task (Wang et al. 2020). Therefore, in the current study, decreased intra-module connections within the subcortical network may relate to motivational and emotional processes, whereas reduced PC may indicate disrupted information integration ability dependent on interactions between subcortex and cortex in individuals with apathy. This assumption needs further examination using specific tasks in the future.

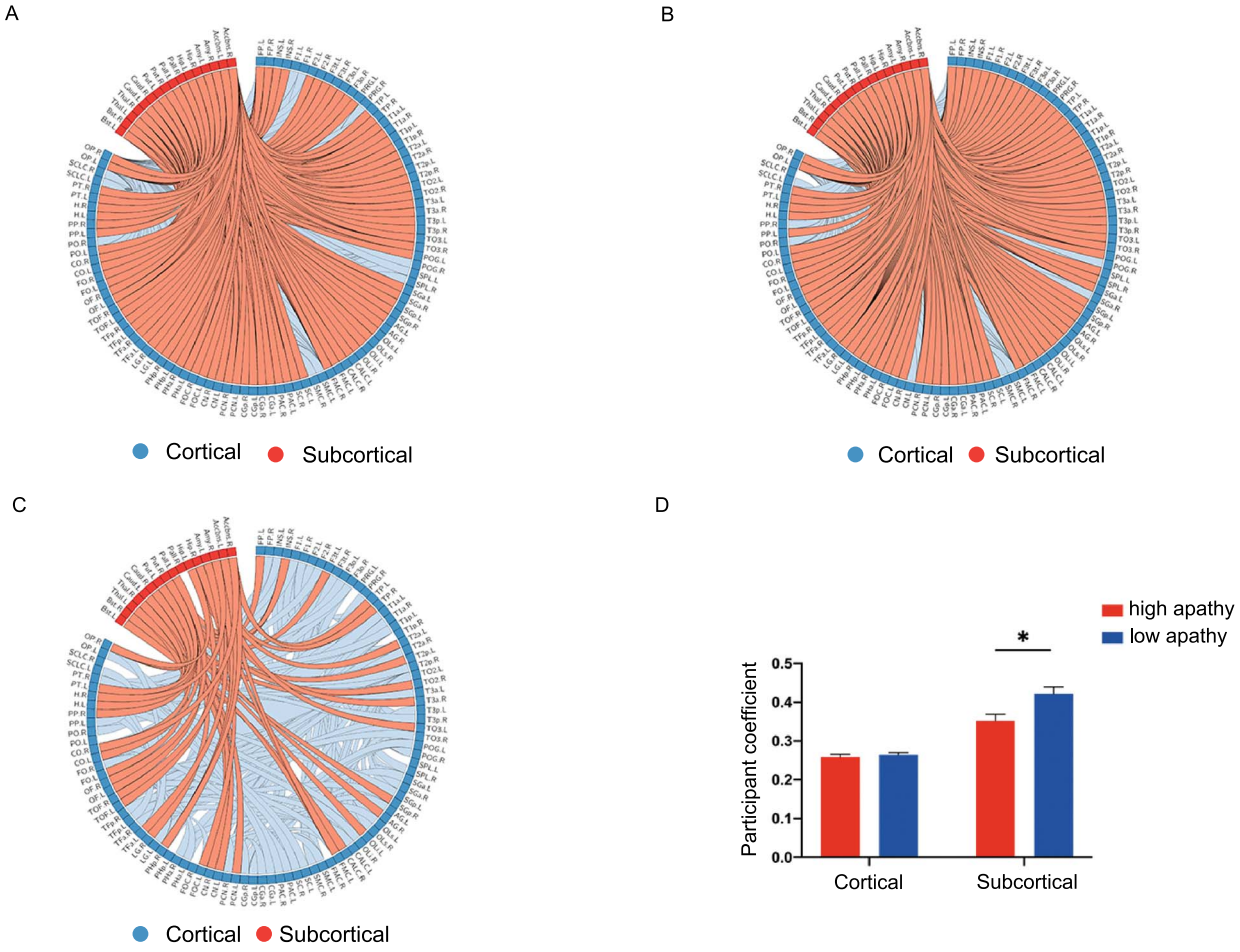

Fig. 2. Intra- and inter-module connections between the cortical and the subcortical networks of (a) high apathy and (b) low apathy groups, as well as (c) the group difference. (d) Average participant coefficient of two groups.

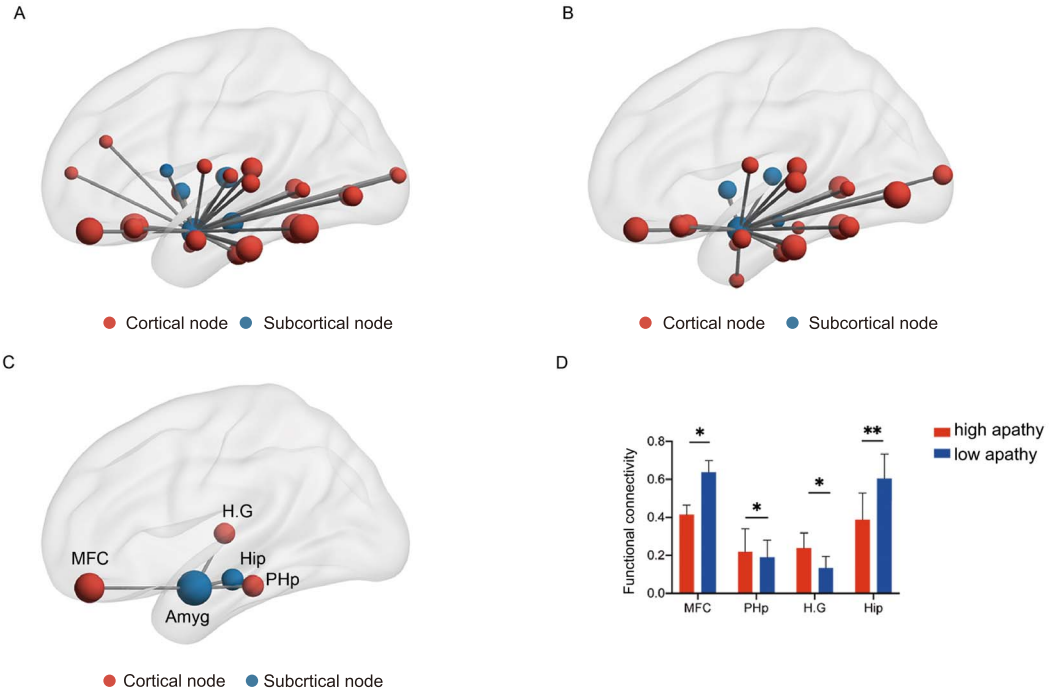

Fig. 3. Functional connectivity between right amygdala and other regions in (a) high apathy group and (b) low apathy group, as well as (c) group difference. Color bar is the *t* value. (d) Average functional connectivity of two groups. Note: $^{*}P < 0.05$, $^{**}P < 0.001$.

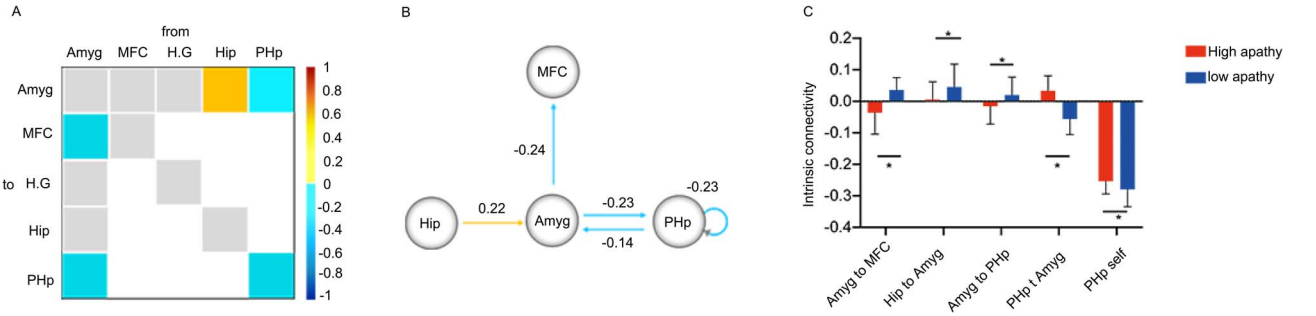

Fig. 4. DCM results. (a) Difference of intrinsic effective connectivity strength of ROIs between high apathy and low apathy group during resting state. The leading diagonal of the matrix showed the values of self-connections. (b) The connectivity model of the amygdala. Positive numbers (and orange arrow) indicate increased inhibition and negative numbers (and blue arrow) indicate disinhibition. (c) Intrinsic connectivity of two groups. Amyg, amygdala; H.G: Heschl gyrus; hip, hippocampus; PHp, parahippocampal gyrus; MFC, medial frontal cortex.

While the amygdala is a key area involved in the motivational processes and emotion regulation (Koob and Volkow 2010), dysfunctional fronto-basal circuits have been shown to contribute to apathy (Levy and Dubois 2006; Bonelli and Cummings 2007; Chase 2011). Together with our network-based results, these findings show altered integration between cortical and subcortical networks in individuals with high apathy, which may be an objective biomarker of apathy.

Altered connectivity of the amygdala as the hub in the brain network of apathy

Group comparisons of nodal topological characteristics showed decreased PC of the amygdala in the high apathy group, suggesting altered inter- and intra-module communications of the amygdala. The amygdala plays an essential role in cognitive-emotional recognition and expression (Gallagher and Chiba 1996; Dolan and Vuilleumier 2003). Dysfunction of the amygdala is closely associated with apathy. Previous studies have shown structural and functional deficits of the amygdala in patients with apathy (Alexopoulos et al. 2013; McLauchlan et al. 2019). The hub of networks can efficiently facilitate information integration and distribution between networks thus may increase vulnerability to disease (Petrovich et al. 2001). Reduced PC of the amygdala reflects less information integration and exchange with other regions, which may contribute to compromised cognitive-emotional processing. These results elucidate the network centric of the amygdala in lack of interest, blunted emotional responses and amotivation in apathy.

Disrupted effective connectivity of the amygdala with hippocampus and medial prefrontal cortex

Enhanced excitatory connectivity from the hippocampus to amygdala while increased bidirectional inhibition between the amygdala and parahippocampal gyrus in the high apathy group suggests altered interactions within the limbic system that involved in emotion regulation. The hippocampus, parahippocampal gyrus and amygdala are key structures of the limbic system with anatomical interconnections (Pitkänen et al. 2000). The amygdala is specialized for the processing of emotional stimuli and experience, while the hippocampal nucleus is essential for context processing and episodic memory, (Petrovich et al. 2001). A core feature of apathy is emotional blunting (Marin et al. 1991). From a pathological perspective, enhanced projections from the hippocampus to amygdala may evoke their negative emotional experience, while increased bidirectional inhibition between the amygdala and parahippocampal gyrus, may in turn suppress emotional processes. Therefore, this abnormal affective pathway may play an important role in lack of interest and diminished emotional involvement in apathy.

Another finding is the significantly increased projection of inhibition from the amygdala to MFC in high apathy group. As shown by previous studies, disturbance of the fronto-subcortical circuit is a core feature of apathy in various diseases (Alexopoulos et al. 2013; Yuen et al. 2015). Medial prefrontal regions play important roles in generating and maintaining incentive, goal-directed behaviors as well as emotional control (Gillan and Daw 2016; Klaasen et al. 2017). These regions receive inputs from the amygdala to provide a route via, which the amygdala modulates the ongoing activity of frontal regions (Pitkänen et al. 2000). Inhibition of this input may reduce detection of motivational information thereby affecting appropriate cognitive processing, which could contribute to amotivation and lack of initiative in apathetic individuals.

Implications for subclinical apathy

Apathy has been well described in neuropsychiatric disorders but is not well understood yet in otherwise healthy individuals. Our observations echo previously described characteristics of apathy both on clinical and subclinical populations. Previous studies with subclinical populations have found amotivation and deficient auto-activation in high apathy individuals to be associated with prefrontal regions and basal ganglia, which are known to be implicated in the expression of apathy in clinical samples (Spalletta et al. 2013; Bonnelle et al. 2016). Taken together, these findings indicate that apathy in subclinical populations could be a marker useful in

the prediction of progression to more severe apathetic conditions. Studies focused on subclinical individuals could contribute to refine current concepts of apathy as an independent clinical syndrome.

A common but important finding was the high correlation between apathy and depression in our sample. Apathy and depression are frequently co-occurred. Indeed, they may be similar in presentation, including diminished interest and anhedonia, but apathy also has more specific symptoms, i.e. motivational, and self-initiation aspects of behavior. Whereas apathy is characterized by indifference, depression is characterized by negative thoughts, hopelessness, and low self-esteem. Previous studies suggest good discriminability between apathy and depression scores in both clinical (Levy et al. 1998; Starkstein et al. 2005) and non-clinical populations (Bonnelle et al. 2016; Pardini et al. 2016) as well as an adequate discriminant validity of the AES (Clarke et al. 2011; Pardini et al. 2016). Moreover, apathy and depression depend on different network properties of the frontal cortex-basal ganglia circuits (Onoda and Yamaguchi 2015). Therefore, it is necessary to specifically evaluate the apathy effect on network properties. By controlling for scores of BDI and SHAPSs, we observed "pure" effect of apathy on cortico-subcortical networks properties, independent of depression and pleasure. Together, these results support the view that apathy and depression are distinctive brain disorders.

In the current study, we used self-report questionnaires, which might be less reliable and valid than clinician-administered instruments (Pardini et al. 2016). Additionally, there was no long-term follow-up, which did not allow us to examine possible causal relationships between apathy and brain network properties.

Conclusions

In summary, we provide the first neuroimaging evidence for altered brain network organization and communication in individuals with apathy. Diminished cortical–subcortical communications as well as disrupted hippocampal-to-amygdala and amygdala-to-MFC pathways jointly characterize the affective and cognitive dysfunctions of apathy. Such alterations of cortical–subcortical network connections could be a risk factor for development to more severe forms of apathy-related clinical conditions.

Author contribution statement

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Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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Data and code availability

Available upon request.

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