NeuroImage: Clinical 20 (2018) 297–304

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Functional and structural connectivity of the amygdala underpins locus of control in mild cognitive impairment

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ARTICLE INFO

Keywords:
Locus of control
Alzheimer's disease signature cortical thickness
Amnestic mild cognitive impairment
Amygdala
Resting-state fMRI
Diffusion tensor imaging

ABSTRACT

Locus of control (LOC) is an important personality trait. LOC over cognitive competency reflects an individual's perceived control of desired cognitive outcomes, which is critical for maintaining successful cognitive aging. It is important to understand the neural substrates of LOC over cognitive competency in older adults, especially for individuals at high risk of dementia. Here, we characterized a cohesive functional and structural connectivity profile underlying LOC among 55 older adults with amnestic mild cognitive impairment (aMCI), combining resting-state functional magnetic resonance imaging and diffusion tensor imaging. The results showed that both functional and structural connectivity between the medial prefrontal cortex and amygdala were significantly correlated with external LOC. The functional connectivity mediated the correlation between structural connectivity and external LOC. In addition, aging-associated neurodegeneration moderated the relationship between structural connectivity and external LOC, showing that the structural connectivity was positively correlated with external LOC in low, but not high neurodegeneration. Our results suggest a critical role of the functional amygdala-frontal network, which may serve as a bridge between its white matter tract and LOC over cognitive competency in groups at high risk for dementia.

1. Introduction

Locus of control (LOC) is an important personality trait, reflecting an individual's perceived control of desired outcomes. There are two types of LOC: internal (i.e., the belief in one's own skills and capabilities in controlling daily life) and external (i.e., the perception of inevitable environmental constraints or powerful others as controls over one's daily life). Cognitively normal older adults often present higher external LOC than their younger counterparts (Lachman, 1986). Aging-associated neurodegeneration, such as dementia, further exaggerates older adults' reliance on external LOC. Older adults with amnestic mild cognitive impairment (aMCI), as an intermediate stage between cognitively normal aging and dementia, tend to have lower internal LOC and higher external LOC than their cognitively normal counterparts (Ren et al., 2017; Trivedi et al., 2016). Notably, higher external LOC is related to ineffective stress management, psychotic experience, and prospective frailty incidence (Sullivan et al., 2017; Twenge et al., 2004; Wu et al., 2004; Elliot et al., 2018, in press), and worsens the link between socioeconomic deprivation and reduced longevity (Turiano et al., 2014). Therefore, addressing the overreliance on external LOC is critical for facilitating successful aging.

To better understand the phenomenon of "overreliance on external LOC" in aging and aging-associated neurodegeneration, recent effort has been made to understand the neural substrates of LOC. Emerging evidence has suggested that frontal-subcortical circuitry, especially the amygdala-related, is associated with perception of control (Declerck et al., 2006; Ren et al., 2017). Previous studies have reported that the amygdala can modulate the efficiency of the executive control network (Fales et al., 2008; Herwig et al., 2007; Krug and Carter, 2010). And executive function has also been found associated with increased

Abbreviations: AD, Alzheimer's disease; ADSCT, Alzheimer's disease signature cortical thickness; aMCI, amnestic mild cognitive impairment; DTI, Diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; MPFC, medial prefrontal cortex; LOC, locus of control; D, mean diffusivity; NV, number of voxels; PIC, Intellectual Aging Contexts; VBM, Voxel-based morphometry

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https://doi.org/10.1016/j.nicl.2018.07.021
Received 8 January 2018; Received in revised form 16 July 2018; Accepted 21 July 2018
Available online 23 July 2018

dopamine release in the amygdala (Fried et al., 2001). Moreover, the perception of lack of control is considered an unsettling and aversive state, which can induce emotional reactivity, thereby activating the amygdala (Whalen, 1998). Therefore, we hypothesized that the amygdala network, especially amygdala-frontal connectivity, may play a crucial role in understanding LOC, which is closely related to executive control and self-regulation.

According to our knowledge, there have been few investigations of the structural substrates of LOC. In young adults, gray and white matter volumes in the anterior cingulate cortex and striatum are significantly correlated with internal LOC (Hashimoto et al., 2015). The only structural MRI study of LOC involving an aging sample was conducted by Pruessner and colleagues, who found that greater hippocampal gray matter volume is related to higher internal LOC in both young and older adults (Pruessner et al., 2005). Brain structural changes (e.g., atrophy, white matter deficits) are common in aging and age-associated neurodegeneration (Sperling et al., 2011). Based on this limited evidence, it is still unclear whether any anatomical substrates can help explain the overreliance on external LOC in the context of age-associated neurodegeneration. To examine structural integrity, diffusion tensor imaging (DTI) provides quantitative information of white matter microstructures by measuring the properties of water diffusion in biological tissues. Common metrics, including mean diffusivity (MD) and fractional anisotropy (FA), can be used to assess the characteristics, such as myelination and microstructural changes, of white matter tracts (Beaulieu, 2002; Le Bihan, 2003). Compared to cognitively normal older adults, cumulative studies show that aMCI has white matter disruptions in the uncinate fasciculus, which connects frontal lobe and amygdala (Fujie et al., 2008; Yu et al., 2017). So far, there is no DTI study on the relationship between white matter integration and LOC change in aging or age-related neurodegeneration.

In the current study, we focused on examining the structural substrates underlying LOC over cognitive competency in older adults with aMCI by combining resting-state fMRI and DTI to analyze the cohesiveness between functional and structural neural connectivity. We hypothesized that functional and white matter connections of the amygdala-frontal network would underpin LOC. Converging evidence shows that functional connectivity/activity reflects its underlying structural integrity, and they may act as a “bridge” between brain structure and behavioral output (Greicius et al., 2009; Leong et al., 2016). Therefore, we speculated that amygdala functional connectivity would mediate the relationship between its structural connectivity and LOC. Since not all individuals with clinical phenotype of aMCI have positive neurodegeneration (McEvoy et al., 2009), we also examined whether the degree of aging-associated neurodegeneration (indexed by Alzheimer's disease signature cortical thickness (ADSCT)) (Jack Jr. et al., 2015; Jack Jr. et al., 2017) would impact the relationships between neural characteristics and LOC.

2. Methods

2.1. Participants

Fifty-five participants with aMCI completed imaging and LOC data collection in the current project. Participants were recruited from university-affiliated memory or geriatric clinics based on the clinical diagnosis of “mild cognitive impairment due to Alzheimer's disease” (Albert et al., 2011). In addition, we also conducted initial cognitive screening using Rey Auditory Verbal Learning Test (for memory) < 7, Montreal Cognitive Assessment (for global cognition) ranging from 18 to 26, and Functional Assessment Questionnaire (for activities of daily living) < 2. For those taking AD medication (i.e., memantine or cholinesterase inhibitors), participants were required to have a stable medication intake for at least 3 months prior to enrollment. Participants were also required to have capacity to give consent based on the research team's assessment, have adequate visual and auditory acuity for testing, be ≥60 years of age, English-speaking, and community-dwelling. Exclusion criteria included presence of severe cardiovascular disease (e.g., chronic heart failure), severe uncontrollable psychiatric disorders (e.g., major depression), and MRI contraindications (e.g., pacemaker, claustrophobia). The study was approved by the university's research subject review board.

2.2. Assessment

LOC was assessed with the Personality in Intellectual Aging Contexts (PIC) Inventory Control Scales-Short Form (Lachman, 1986). The scale includes three 12-item subscales: internal (reflecting internal LOC), chance, and powerful others (the latter two reflecting external LOC). Internal LOC assesses perceived control over one's intellectual competence. The other two subscales assess the perception that environment (chance) or individuals (powerful others) are responsible for one's cognitive capabilities. Responses were made on a 6-point scale, from 1 (strongly agree) to 6 (strongly disagree). Items of a subscale were averaged so that higher scores in all subscales indicated higher levels of LOC. We used averaged scores of chance and powerful others to reflect external LOC (Ren et al., 2017; Zahodne et al., 2015). Cronbach's α was 0.68 for internal LOC and 0.81 for external LOC in the present study. Sample characteristics and demographics are presented in Table 1. Neither internal nor external LOC was significantly related to age, sex, education, or any domains of cognitive function (Supplementary Table S1).

2.3. Imaging data acquisition

Imaging data were collected at the Rochester Center for Brain Imaging using a 3 T Siemens TrioTIM scanner (Erlangen, Germany) equipped with a 32-channel receive-only head coil transmission. The fMRI scan began with a MPRAGE scan (TR/TE = 2530/3.44 ms, TI = 1100 ms, FA = 7, matrix = 256 × 256, resolution 1 × 1 × 1 mm, slice thickness = 1 mm, 192 slices). The resting-state fMRI data were collected using a gradient echo-planar imaging (EPI) sequence (TR/TE = 2500 ms/30 ms, FA = 90, slice thickness = 4 mm, matrix = 64 × 64, 4 × 4 mm in-plane resolution, 42 axial slices, volumes = 100). Participants were required to keep their eyes open during the resting-state scanning (4.2 min). Diffusion-weighted images were obtained using EPI sequence (TR/TE = 8900 ms/86 ms, 70 axial slices, matrix = 128 × 128, 60 diffusion weighting images b = 1000 s/mm^2, 10 non-diffusion weighting images b = 0, bandwidth = 1502 Hz/vx, voxel size 2 × 2 × 2 mm).

2.4. Brain atrophy

Voxel-based morphometry (VBM) analysis was performed to generate a whole-brain gray matter map using SPM8 (http://www.fil.ion.

Table 1
Demographics and clinical characteristics (n = 55).

Age, M (SD)	74.47 (7.67)
Male, n (%)	32 (58.2)
Years of education, M (SD)	16.46 (2.51)
Taking AD Medication, n (%)	6, (10.9)
MOCA, M (SD)	24.35 (2.44)
BVMT-R learning, M (SD)	41.42% (31.67%)
BVMT-R delayed recall, M (SD)	25.22% (31.31%)
Executive function, M (SD)	−0.14 (0.47)
Internal LOC, M (SD)	5.15 (0.56)
External LOC, M (SD)	2.39 (0.65)

Note. SD, standard deviation; AD: Alzheimer's disease; MOCA: Montreal Cognitive Assessment; BVMT-R: Brief visuospatial memory test-revised (participants here had a percentile below the average of age- and education-adjusted population norm); LOC: Locus of control.

ucl.ac.uk/spm/). Briefly, the structural images were segmented into gray matter, white matter, and cerebrospinal fluid. After an initial affine registration of the gray matter map into the MNI space, the gray matter images were nonlinearly warped using DARTEL (Ashburner, 2007), a toolbox which implements a fast diffeomorphic registration algorithm. Finally, the gray matter map was resliced to a 3 × 3 × 3 mm grid and smoothed with Gaussian kernel (FWHM 8 mm) to match the functional image of each subject. The gray matter volume was then applied as a covariate for controlling brain atrophy in functional connectivity related analyses.

2.5. Aging-associated neurodegeneration score

Aging-associated neurodegeneration, one of the major aging-associated pathophysiology biomarkers, was assessed using the ADSCT, which averaged cortical thickness of bilateral inferior and middle temporal lobes, entorhinal cortex, and fusiform gyrus, with lower values indicating more severe neurodegeneration (Jack Jr. et al., 2015; Jack Jr. et al., 2017). Cortical thickness was calculated using FreeSurfer image analysis suite v5.1.0 (http://surfer.nmr.mgh.harvard.edu/). The pipeline includes skull stripping, registration, and cortical surface construction (Fischl and Dale, 2000). Automated cortical parcellation was performed using the Desikan-Killiany Atlas, which labels 34 cortical parcellations in each hemisphere (Desikan et al., 2006).

2.6. fMRI data analysis

The fMRI data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF v2.3) (Chao-Gan and Yu-Feng, 2010) based on SPM8. For each participant, imaging data were corrected for slice timing and head-motion, co-registered to their own structural image, and normalized to the Montreal Neurological Institute (MNI) standard space. All processed fMRI images were resampled to 3 × 3 × 3 mm. After that, all data were smoothed using Gaussian kernel (FWHM 8 mm), underwent linear trend removal, and filtered with a band-pass filter of 0.01 to 0.08 Hz. Prior to functional connectivity analysis, nuisance covariates were regressed out at individual subject level, including 6 head motion parameters, white matter signal, and cerebrospinal fluid signal (Fox et al., 2006; Kelly et al., 2008). The head motion of each participant was < 2 mm or 2 degrees in the present study. However, given the commonality of head motion in older age and its confounding effect on the functional connectivity analysis (Power et al., 2013; Van Dijk et al., 2012), we still considered head motion as a covariate in later statistical analyses involving functional connectivity. The mean displacement of head motion was computed as the root-mean-square of the translation parameters [displacement = square root $(x^2 + y^2 + z^2)$; x (left/right), y (anterior/posterior), and z (superior/inferior) directions] and controlled in the following group analysis.

To define the amygdala network, bilateral amygdala were collectively selected as a single seed based on the Automated Anatomical Labeling (AAL) template (Tzourio-Mazoyer et al., 2002). The averaged fMRI time series within the amygdala mask was extracted to correlate with all of the voxels across the entire brain. Subsequently, individuals' correlation coefficient map was Fisher's r-to-z converted. To examine the correlation pattern between amygdala functional connectivity and LOC, linear regressions were applied for internal and external LOC separately, controlling for gray matter volume and head motion. The correlation maps were then generated with a threshold of $p < 0.05$ (FWE correction). After we identified the relationship between amygdala functional connectivity and LOC, the correlated brain region [in this case, medial prefrontal cortex (MPFC); additional details are presented in the Results section] was applied as a mask for following functional and structural connectivity analyses.

2.7. DTI data analysis

The DTI data were preprocessed using FSL v5.0.9 (http://www.fmrib.ox.ac.uk/fsl). Eddy current distortion and head movement were corrected using DTIFIT. Brain extraction and brain mask generation were completed with a fractional intensity threshold of 0.25 using BET. Individual brain images were visually inspected for signal dropout, artifacts, and other distortions. FA and MD images were calculated and nonlinearly registered to the MNI standard space.

Since only MPFC-amygdala functional connectivity was significantly correlated with external LOC (see the Results section), unconstrained probabilistic tractography was conducted to examine the anatomical connections between amygdala and MPFC using the FMRIB diffusion tool (Behrens et al., 2007). Probabilistic tractography was performed using FMRIB's diffusion toolbox in FSL5.0.9 (FDT v2.0, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). BEDPOSTX was used to calculate 5000 iterations at each voxel with a curvature threshold of 0.2, a step length of 0.5, and a maximum number of 2000 steps (Behrens et al., 2007). The connection probability was defined by the number of tracts that reach a target (MPFC) from a given seed (amygdala). Since the threshold of probabilistic tractography remains an unsolved statistical issue (Morris et al., 2008), we used FSLstats to identify the voxels with the maximum connectivity value within individuals' connectivity map with thresholds at 50%, 25%, and 15% of the maximum connectivity value (Bennett et al., 2011; Khalsa et al., 2014). Compared to previous studies that used a constant proportion of the total number of permutations for all participants, the proportional thresholds used here considered individual differences in tract strength. To assess the strength of structural connectivity, three indices were calculated within the tract, including the number of voxels (NV) beyond each threshold, FA, and MD.

2.8. Statistical analysis

All statistical analyses were performed using SPSS 22.0. Pearson's correlation was applied to examine relationships between structural connectivity, functional connectivity, and LOC. Mediation analysis was used to assess whether functional connectivity mediated the relationship between structural connectivity and LOC using macro PROCESS (http://www.processmacro.org). Moderation analysis was applied to examine the interaction effect between ADSCT and structural or functional connectivity on LOC using macro PROCESS. Age and education were controlled across all analyses. For any analysis involving functional connectivity, head motion and the mean gray matter volume of bilateral amygdala and MPFC were also controlled.

3. Results

3.1. Amygdala functional connectivity and LOC

Taking bilateral amygdala as a seed, whole brain voxel analysis was applied to determine the regions whose functional connectivity with amygdala were significantly related to internal or external LOC. The connectivity between MPFC (MNI coordinate: 12, 48, 6, cluster size: 60 voxels, corrected $p < .05$) and amygdala was positively correlated to external LOC ($r_{48} = 0.55$, $p < .001$), controlling for gray matter volume and head motion (Fig. 1). No brain regions' functional connectivity with the amygdala had significant correlation with internal LOC.

3.2. Amygdala structural connectivity and external LOC

Based on the MPFC-amygdala functional connectivity, the MPFC-amygdala structural tract was reconstructed using probabilistic tractography (Fig. 2A). Since one of the subjects has extremely high NV (NV = 146), this subject was excluded as an outlier in the NV related

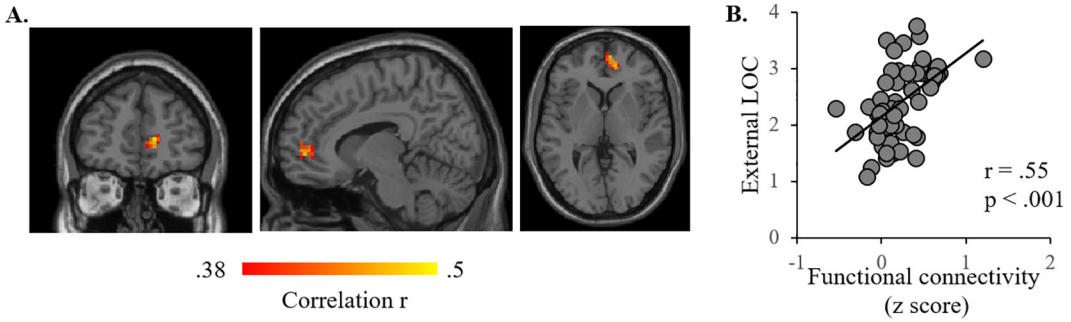

Fig. 1. The MPFC-amygdala functional connectivity linking to LOC. A) The functional connectivity between the amygdala and MPFC was significantly correlated with external LOC (corrected $p < .05$); B) The scatterplot of relationship between the MPFC-amygdala functional connectivity and external LOC.

analysis. The MPFC-amygdala functional connectivity was significantly correlated with NV at a threshold of 50% ($r_{47} = 0.40$, $p = .004$), 25% ($r_{47} = 0.36$, $p = .012$), and 15% ($r_{47} = 0.31$, $p = .029$), and significantly correlated with MD at the threshold of 50% ($r_{48} = -0.28$, $p = .046$), but not 25% ($r_{48} = 0.22$, $p = .12$) or 15% ($r_{48} = 0.23$, $p = .11$) controlled for age, education, head motion, and gray matter volume (Fig. 2B). FA was not significantly correlated with functional connectivity or external LOC (data is not shown). In the following analyses, we used the threshold of 50% from DTI that showed the significant correlations with both NV and MD. There were significant

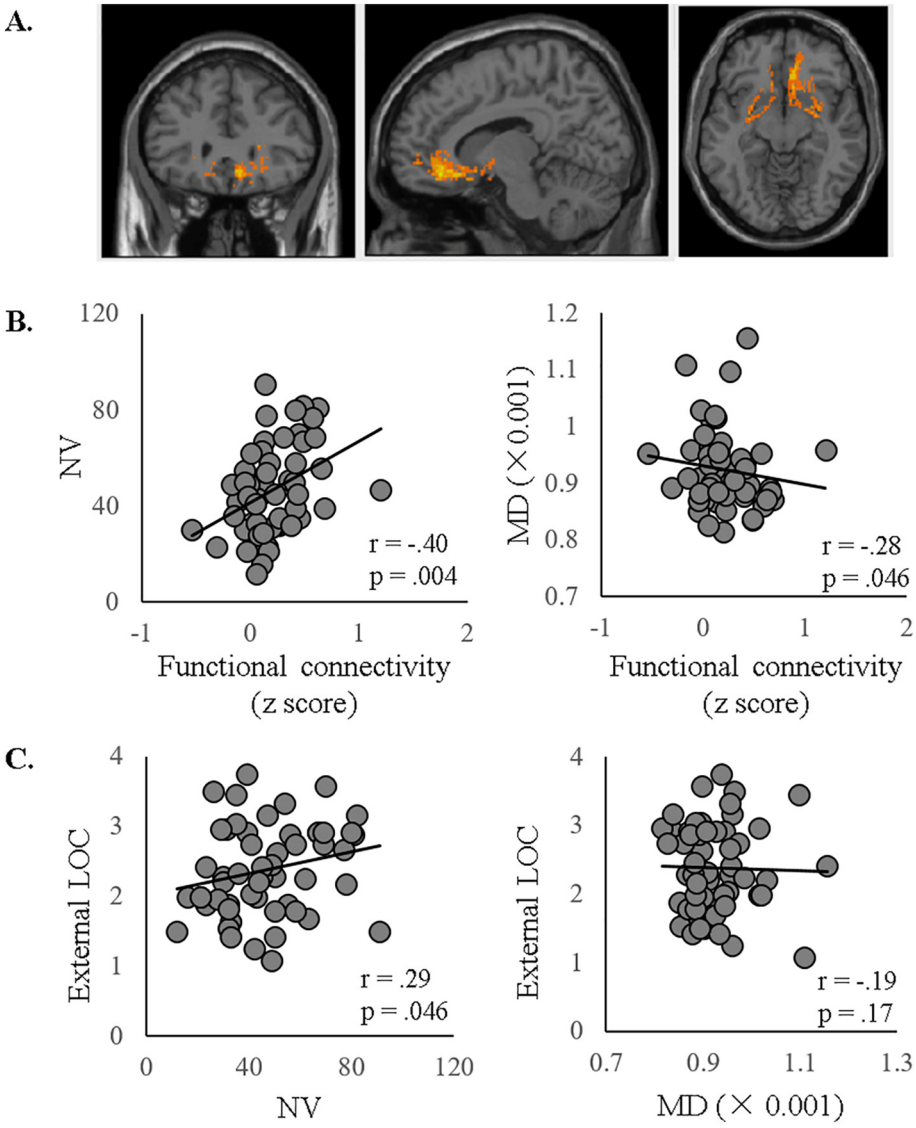

Fig. 2. The relationships between functional and structural connectivity of the MPFC-amygdala network and external LOC. A) Based on the findings of functional connectivity analysis, the probabilistic tractography was applied to generate the white matter connectivity between MPFC and amygdala; B) The scatterplot of relationship between MPFC-amygdala functional and structural connectivity; C) The scatterplot of relationship between MPFC-amygdala structural connectivity and external LOC.

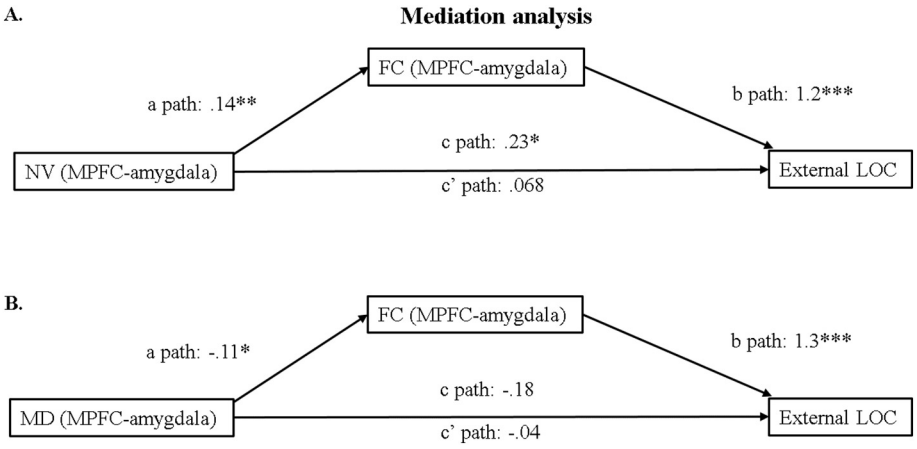

Fig. 3. Mediation analysis of the relationship between MPFC-amygdala network and external LOC. A) Functional connectivity mediated the relationship between NV and external LOC. B) Functional connectivity mediated the relationship between MD and external LOC. Note. a, b, and c' reflects direct effect (β); c reflects total effect (β); *p < .05; **p < .01; *** p < .001.

correlations between external LOC and NV (r_{50} = 0.29, p = .046), but not MD (r_{51} = −0.19, p = .17) controlled for age and education (Fig. 2C). Additionally, the internal LOC was not correlated with MD (r51 = 0.14, p = .33) or NV (r_{47} = −0.085, p = .55).

3.3. Functional connectivity mediates the relationship between structural connectivity and external LOC

Mediation analysis was applied to examine whether functional connectivity would mediate the relationship between the white matter integrity and external LOC controlled for age, education, head motion, and gray matter volume. We found a significant mediation effect of functional connectivity in the relationship between NV (B (SE) = 0.23 (0.068), 95% CI: [0.06, 0.29], p < .05), as well as MD (B (SE) = −0.18 (−0.04), 95% CI: [−0.34, −0.0027], p < .05), and external LOC (Fig. 3).

3.4. Aging-associated neurodegeneration moderates the relationship between structural connectivity and external LOC

According to cortical thickness analysis, the ADSCT score in the entire sample ranged from 2.39 to 2.94 (Mean = 2.67, SD = 0.14). There were significant correlations between ADSCT and MD (r_{51} = −0.32, p = .021), as well as amygdala gray matter (r_{51} = 0.48, p < .001), but not between ADSCT and NV (r_{50} = 0.08, p = .56), MPFC gray matter (r_{51} = −0.021, p = .89), functional connectivity (r_{48} =. -0.46, p = .75), or external LOC (r_{51} = 0.03, p = .82) controlled for age and education.

Moderation analysis was applied to examine the role of ADSCT in relationship between structural/functional connectivity and external LOC. The interaction between ADSCT and NV was significant (β = 2.10, t_{48} = 2.78, p = .008). Participants with high ADSCT [higher than 2.81 (mean + 1SD)] showed a significant positive correlation between NV and external LOC (β = 0.44, t_{48} = 3.29, p = .002), while those with low ADSCT [lower than 2.53 (mean-1SD)] showed no correlation between NV and external LOC (β = −0.16, t_{48} = −0.95, p = .35) (Fig. 4). There was no moderation effect of ADSCT on relationships of functional connectivity or MD and external LOC.

4. Discussion

To the best of our knowledge, this is the first study characterizing cohesive functional and structural connectivity of LOC, specifically in a group at high risk for dementia. We revealed a relationship between functional connectivity of the MPFC-amygdala and its corresponding anatomical connectivity (indexed by both NV and MD), which in turn was positively correlated with external LOC. Our mediation analysis showed that the MPFC-amygdala functional connectivity mediated the relationship between NV/MD of the same network and external LOC, supporting the idea that functional connectivity may serve as a "bridge" between its structural connectivity and behavioral output. Moreover, less severe aging-associated neurodegeneration (indexed by higher ADSCT values) was related to higher white matter integrity (indexed by lower MD); and a moderation analysis showed that ADSCT moderated the correlation between NV and external LOC, suggesting that neurodegeneration may disrupt the structural connectivity underpinning external LOC.

As an important component of the limbic system, the amygdala and its functional networks are closely related to multiple personality traits, including self-esteem, extraversion, and neuroticism (Canli et al., 2002; Cremers et al., 2010; Pruessner et al., 2005; Wang et al., 2016). Here, we found both the functional and structural connectivity of MPFC-amygdala to be associated with external LOC. The MPFC is known to be a neuroanatomical node processing self-relevant information, such as value of the self (D'Argembeau et al., 2012; Denny et al., 2012). The MPFC-amygdala connectivity may therefore reflect an anatomical substrate that synthesizes information from multiple resources – value of the self, emotional responses to experience related the controllability, and cognitive appraisal of controllability. Interestingly, the relationships between the amygdala-frontal functional connectivity and external LOC were different from those observed in our prior study that combined aMCI patients with cognitively healthy older adults (Ren et al., 2017). For external LOC, the correlation was positive with the functional connectivity of ventral frontal region (MPFC)-amygdala in the current study, while the correlation was negative with the functional connectivity of the dorsal frontal regions (middle cingulate cortex and superior frontal gyrus)-amygdala in our previous study. Accumulative studies suggest functional distinctions of ventral vs. dorsal prefrontal cortex in emotion regulation and autonomic response vs. executive control (Etkin et al., 2011; Kim et al., 2011; Koenigs and Grafman, 2009; Schmitz and Johnson, 2006). Moreover, the dorsal and ventral frontal regions haven been found affected by neurodegeneration differently. Specifically, it has been found hypometabolism/reduced neural function in dorsal frontal regions while hypermetabolism/enhanced neural function in ventral frontal regions in AD associated neurodegeneration (Sultzer et al., 2003; Zhang et al., 2015). These divergent findings may be due to different sample characteristics (i.e., using a cognitively diverse sample in our previous study compared to studying aMCI alone in the current study), but both of them may shed light on the altered LOC in the neurodegenerative process. Of note, we did not find any neural correlates of internal LOC in the current study; in our previous study, however, we found a positive relationship between internal LOC and anterior cingulate cortex/middle frontal gyrus (Ren et al., 2017). It may be due to the difference in the sample characteristics as well. Compared to cognitively normal counterparts, the aMCI group had lower internal LOC and relied mostly on external LOC

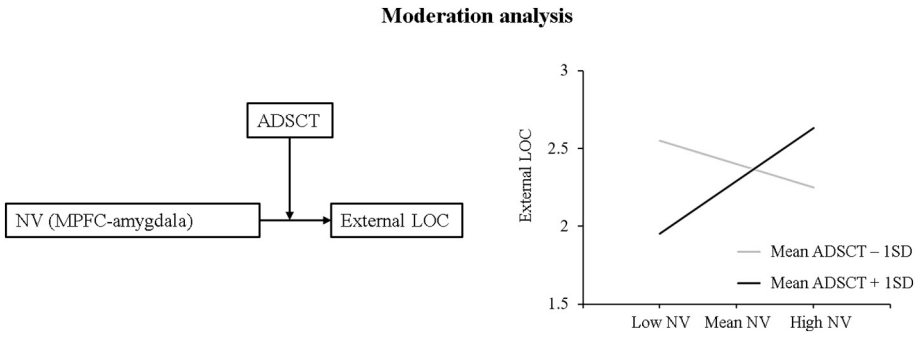

Fig. 4. ADSCT moderated the relationship between NV and external LOC. Only high ADSCT level (Mean ADSCT + 1SD) showed significant positive correlation between NV and external LOC.

(Ren et al., 2017; Trivedi et al., 2016). Hence, it may be difficult to detect the neural linkage of internal LOC in an aMCI group alone due to their relatively small variation of internal LOC.

Here the structural substrate was defined based on the functional connectivity of MPFC-amygdala underlying external LOC using probabilistic tractography. Relative to deterministic methods, probabilistic algorithms are better for tracking regions with low FA, which is suitable for detecting the tracts of interest between the gray matter regions (i.e., MPFC and amygdala) in the present study. Of note, since thresholding probabilistic tractography remains an unsolved issue (Morris et al., 2008), three different proportional thresholds (50%, 25%, and 15% of the maximum tract value) were calculated for the strength of structural connectivity. Despite using a constant threshold for all individuals, the proportional threshold accommodates individual differences in connectivity values for the white matter tract, which in turn maximizes tract size and quality (Bennett et al., 2011; Khalsa et al., 2014). Although we selected the threshold at 50% of the maximum connectivity value in the following analysis, the patterns of correlation between structural connectivity and functional connectivity or external LOC were similar across 50%, 25%, and 15%, which reflects the robustness of our analysis.

More importantly, our results suggest that functional connectivity of the MPFC-amygdala network may link its structural connectivity with external LOC. Earlier evidence has shown that individuals with aMCI often over activate frontal regions and recruit extra networks to compensate for cognitive dysfunction despite deficits in brain structure (Buckner, 2004; Liang et al., 2011), suggesting that brain function plays a critical role in linking neurodegeneration-related structural changes to cognitive function. Interestingly, we did not find any significant relationship between LOC and FA, suggesting the complexity of white matter microstructures in underlying different brain functions. In consistent with our findings, MD was found to be a better index for explaining biological variance associated with personality traits (Laricchiuta et al., 2014). Another personality study found that MD is associated with several key aspects of psychopathology in borderline personality disorder and attention-deficit hyperactivity disorder compared to FA, which may be due to crossing fibers selectively affecting FA but not MD (Rusch et al., 2007). Taken together, we speculate that NV and MD may be more sensitive for describing white matter integrity as a link to brain function underlying LOC.

In addition, our results showed that aging-related neurodegeneration impacts the relationship between the strength of structural connectivity and external LOC. The significant positive correlation between structural strength and external LOC only existed in those with less severe age-associated neurodegeneration (i.e., high ADSCT group), indicating that neurodegeneration may disrupt the anatomical substrates linking to external LOC. In contrast to the interaction effect between ADSCT and structural connectivity, we did not find an effect between ADSCT and MPFC-amygdala functional connectivity in relation to external LOC. In line with these findings, previous studies have suggested that structural deficits occur earlier than functional change in the amygdala in neurodegeneration (Douaud et al., 2013; Fujie et al., 2008; Yao et al., 2013). Furthermore, neural compensation commonly observed in the frontal regions may moderate the functional disruptions of relevant networks (Bosch et al., 2010; Gould et al., 2006; Stern, 2012). Regardless, although ADSCT value is known to related to the progression of Alzheimer's disease (AD), it is not an AD-specific pathology marker (Jack Jr. et al., 2015; Jack Jr. et al., 2015). To understand how specific the current findings are for those affected by AD, AD-specific pathology (e.g., amyloidosis) needs to be considered in future research.

Finally, we need to acknowledge several limitations in the current study. First, we focused on the relationship between LOC and the amygdala network, which may ignore other relevant brain regions. Previous studies have reported other brain regions or networks, such as the hippocampus, anterior insula, and frontal-striatum circuit (Hashimoto et al., 2015; Omura et al., 2005; Pruessner et al., 2005) may be related to LOC. Therefore, examining these networks in the future research may complement our findings. Second, as discussed earlier, the relatively narrow range of LOC in the current study from a single aMCI group could influence detection of the correlation between LOC and the amygdala network. Further analysis of the left and right amygdala networks separately showed similar associations with external LOC, but not internal LOC (see Supplementary Fig. S1). However, involving cognitively normal aging and AD groups needs to be considered in future research to better examine the alteration of LOC in neurodegeneration, especially its hemispheric lateralization.

In conclusion, the current study identified that amygdala-MPFC functional connectivity mediated the relationship between its structural connectivity and external LOC in groups at high risk for dementia. Aging-associated neurodegeneration appears to affect the structural, but not necessarily functional substrate underlying LOC. Recently, the longitudinal effect of personality on AD progression has attracted substantial attention (Terracciano et al., 2017). Given the potential neural profiles underlying LOC, as well as known overreliance on external LOC in groups at risk for dementia, tracking the longitudinal changes of LOC may add another layer to the current understanding of the relationship between personality and dementia, especially AD.

Acknowledgement

No conflict of interest to be disclosed. Data collection is funded by R01 NR015452 to F. Lin.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.07.021.

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