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Amygdala functional connectivity is associated with locus of control in the context of cognitive aging

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ABSTRACT

Locus of control (LOC) measures the extent to which individuals perceive control over their lives. Those with a more "internal" LOC feel self-sufficient and able to determine important aspects of their own future, while those with a more "external" LOC feel that their lives are governed by events beyond their control. Reduced internal LOC and increased external LOC have been found in cognitive disorders, but the neural substrates of these control perceptions are yet unknown. In the present study, we explored the relationship between amygdala functional connectivity and LOC in 18 amnestic mild cognitive impairment (MCI) and age-, sex-, and education-matched, 22 cognitively healthy controls (HC). Participants completed cognitive challenge tasks (Stroop Word Color task and Dual 1-back) for 20 min, and underwent resting-state functional magnetic resonance imaging immediately before and after the tasks. We found significantly lower internal LOC and higher external LOC in the MCI group than the HC group. Compared to HC, MCI group showed significantly stronger positive associations between internal LOC and baseline right amygdala connections (including right middle frontal gyrus and anterior cingulate cortex), and stronger negative associations between internal LOC and change of these right amygdala connections. Across all participants, external LOC explained the relationships between associations of another set of right amygdala connections (including middle cingulate cortex and right superior frontal gyrus), both at baseline and for change, and performance in the cognitive challenge tasks. Our findings indicate that the right amygdala networks might be critical in understanding the neural mechanisms underlying LOC's role in cognitive aging.

1. Introduction

Locus of control (LOC) reflects the extent to which individuals see internal or external factors as influencing their desired outcomes. Internal LOC is defined as the belief in one's own skills and capabilities in controlling life, while external LOC is the perception of inevitable environmental constraints or powerful others as controls over one's life (Lachman, 1986). Numerous studies have contributed to distinguishing the two types of LOC and their distinct outcomes (Rashid, 2016). For example, higher internal LOC has been associated with better life outcomes, including better memory performance (Lachman, 2006), less disability (Gruber-Baldini et al., 2009), greater mental health and well-being (Johnson et al., 2009), and positively perceived health status (Berglund et al., 2014). Meanwhile, external LOC has been associated with more negative outcomes, such as high risk for anxiety and poor mobility in older adults (Beekman et al., 1998; Sartori et al., 2012). Aging seems to particularly affect internal LOC but not external LOC, and lower internal LOC in older adults is related to more memory problems and physical disabilities (Lachman, 2006). Conversely, compared with young adults, older adults often present higher external LOC (Lachman, 1986). These findings indicate that aging is closely related to change of LOC, which can affect health outcomes in old age (Caplan and Schooler, 2003; Fauth et al., 2007; Infurna et al., 2011; Krause and Shaw, 2000). Given the dissociated trajectories and impacts of internal vs. external LOC, addressing LOC may provide a pathway for maintaining successful aging.

More recently, efforts have been made to understand the association between neurologic disorders and LOC. In patients with Parkinson's

Abbreviations: ACC, anterior cingulate cortex; AD, Alzheimer's disease; FC, functional connectivity; HC, healthy control; IIVRT, intraindividual variability in reaction time; LOC, locus of control; MCC, mid-cingulate cortex; MCI, mild cognitive impairment; MNI, Montreal Neurological Institute; MOCA, Montreal Cognitive Assessment; PFC, prefrontal cortex; RAVLT, Rey's Auditory Verbal Learning Test; RMFG, right middle frontal gyrus; RSFG, right superior frontal gyrus; Rs-fMRI, resting state functional magnetic resonance imaging

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disease, greater internal LOC is associated with less disability (Gruber-Baldini et al., 2009). Emerging studies also suggest that traits related to LOC may help differentiate individuals at risk for AD from older cognitively normal populations. Conscientiousness, which reflects a sense of personal responsibility similar to internal LOC, and neuroticism, which often indicates vulnerability and helplessness similar to external LOC, have emerged as potent protective and risk factors, respectively, for the incidence of dementia (Duberstein et al., 2011; Low et al., 2013). Higher conscientiousness and lower neuroticism also appear to delay or prevent the onset of significant dementia symptoms in the presence of AD pathology (Terracciano et al., 2013). Similar to cognitive aging literature (Lachman, 2006), within the context of neurological disorders, internal LOC might provide individuals with a sense of agency or influence over their ability to manage declining cognition (e.g., developing effective coping strategies), facilitating adaptation. So far, however, no study has explored the neural mechanism of LOC, especially under cognitive demand in a group with probable AD-associated neurodegeneration. Noticeably, amnestic mild cognitive impairment (MCI), a subtype of MCI with compromised episodic memory, is considered a preclinical phenotype of AD (Eklund et al., 2016). A thorough mechanistic investigation of LOC may aid in the development of effective preventive strategies to address cognitive decline in this group.

The amygdala, a subcortical structure in the fronto-limbic system, may be critical for understanding the neural mechanism of LOC. There are multiple psychological, emotional, or cognitive links to amygdala, such as emotion regulation (Labuschagne et al., 2010; Siegle et al., 2007), neuroticism (Cremers et al., 2011; Lu et al., 2014; Omura et al., 2005), and acute stress regulation (van Marle et al., 2010; van Marle et al., 2009), including in AD patients (Poulin et al., 2011). Moreover, dysfunction of the amygdala has been implicated in personality disorders involving stress reactivity (Meyer-Lindenberg et al., 2009; New et al., 2007), as well as amnestic MCI (Hasselbalch et al., 2008). In addition to the amygdala, accumulated evidence suggests that stronger functional connectivity (FC) between the amygdala and other brain regions, such as prefrontal cortex (PFC), is associated with less social anxiety (Blackford et al., 2014), lower neuroticism scores (Cremers et al., 2010), reduced negative affect (Banks et al., 2007), and better cognitive control (Fine et al., 2001; Ochsner and Gross, 2005). All of these psychosocial, cognitive, and affective factors have been linked to LOC in the literature (Carden et al., 2004; Cooklin et al., 2013). Taken together, we speculate that the amygdala network may be important in understanding the neural substrates of LOC, including those at risk for AD.

In the present study, we compared the internal vs. external LOC in the context of everyday cognition (e.g., handling finance, playing cross-word puzzle) between participants with amnestic MCI and their age-, sex-, and education-matched healthy counterparts (HC) and examined the relevant neural mechanism with resting-state functional magnetic resonance imaging (rs-fMRI). In addition to determining the static neural correlates of LOC, we also employed a cognitive challenge task protocol to examine whether the LOC relevant neural correlates would link to cognitive performance in the cognitive challenge tasks. Of note, previous studies showed that brain networks derived from rs-fMRI can be immediately modulated by short-term cognitive demands seen in the cognitive challenge tasks, (e.g., Van Dijk et al., 2012).

2. Methods

2.1. Participants

Forty participants (22 HC and 18 MCI) completed the study. Participants with amnestic MCI were recruited from university-affiliated memory clinics using the clinical diagnosis of “mild cognitive impairment due to Alzheimer's disease” (Albert et al., 2011). All participants had deficits in memory based on a comprehensive neuropsychological battery, but intact basic activities of daily living and absence of dementia using NINCDS-ADRDA criteria per assessments. Participants had to be stable on Alzheimer's disease medication (i.e., memantine or cholinesterase inhibitors) for 3 months prior to enrollment. Age-, sex-, and education-matched HC participants without self-reported history of dementia or MCI were recruited from the community (e.g., senior centers). In addition, participants from both groups were 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 inflammatory disease (e.g., irritable bowel syndrome), severe uncontrollable psychiatric disorders (e.g., major depression), and MRI contraindications (e.g., pacemaker, claustrophobia). The two groups significantly differed in their global cognition (measured using Montreal Cognitive Assessment, MOCA) and episodic memory (measured using delayed recall from the Rey's Auditory Verbal Learning Test, RAVLT) (see Table 1). The study was approved by the university's research subject review board.

Table 1
Demographics and clinical characteristics of MCI and HC group.

	HC (n = 22)	MCI (n = 18)	t or χ^2 test (p value), df
Age, M (SD)	71.23 (9.61)	74.44 (10.60)	−1.01 (.32), 38
Years of education, M (SD)	15.64 (2.50)	15.39 (2.87)	.29 (.77), 38
Male, n (%)	8 (36.4)	8 (44.4)	.27 (.60), 1
Memantine/cholinesterase inhibitor	–	3 (16.7)	–
MOCA, M (SD)	26.14 (2.67)	24.17 (2.55)	2.35 (.024), 38
Delayed recall, M (SD)	9.24 (2.7)	5.78 (4.66)	2.78 (.010), 37
Internal LOC, M (SD)	5.33 (.52)	4.64 (.96)	2.87 (.007), 38
External LOC, M (SD)	2.09 (.72)	2.95 (.82)	−3.54 (.001), 38
IIVRT, M (SD)	.31 (.06)	.39 (.06)	−4.11 (< .001), 37

Note. HC, healthy control; MCI, mild cognitive impairment; MOCA: Montreal Cognitive Assessment; LOC, locus of control; IIVRT, intra-individual variability in reaction time; LOC, locus of control.

2.2. Design and procedure

The present study was cross-sectional, consisting of two sessions within a two-week window. The first session entailed psychological interviews. The second session included a 20-min series of cognitive tasks and two rs-fMRI scans immediately before and after the tasks. The cognitive tasks included two commonly used computerized tasks: Stroop Color Word (inhibitory control) and Dual 1-back task (working memory). For the Stroop task, participants were shown serial colored words on the screen, and asked to judge the color of the word regardless of the meaning of the word as quickly and accurately as possible. For the Dual 1-back task, participants were shown an English letter on the screen, and asked to judge if the current stimulus matched the letter and position of the previous one as quickly and accurately as possible. For both tasks, feedback was displayed after participant responded to an individual trial. Reaction time (RT) and accuracy from the two tasks were recorded for further analysis. Each of the tasks lasted 10 min, and the order of the two tasks was randomized across participants. Instructions and practice were provided before each of the formal tasks.

2.3. Measures

2.3.1. LOC assessment

LOC was assessed with the Personality in Intellectual Aging Contexts (PIC) Inventory Control Scales-short form (Lachman, 1986).

The measure included three 12-item subscales: internal (reflecting internal LOC), chance, and powerful others (the latter reflecting external LOC). Internal LOC assesses the perception of control over an individual's intellectual competence. The other two subscales assess the perception that environmental (chance) or others (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 the chance and powerful others subscales were reversely coded. Items of a subscale were averaged so that higher scores in all subscales indicated higher levels of LOC. We used averaged scores of the two subscales of chance and powerful others to reflect external LOC (Zahodne et al., 2015). The Cronbach's α for the three scales were .83, .74, .86, respectively, for the entire sample in the present study. Of note, the shared similarity between internal and external LOC was $R^2 = 34.6\%$ for MCI group and 24.7% for HC group. A large difference between internal and external LOC required them to be analyzed separately.

2.3.2. Intra-individual variability in reaction time (IIVRT)

IIVRT to cognitive tasks, which measures the within-person fluctuations across trials, was used to assess the cognitive task performance. Compared to mean RT or response accuracy, IIVRT is more valid in reflecting cognitive capability (Hultsch et al., 2000; Strauss et al., 2002; Wang et al., 2014), and considered a sensitive marker for cognitive decline in aging and neurodegenerative disorders (Bielak et al., 2010; Jackson et al., 2012). For each task (Stroop or 1-back), the first three trials were excluded to avoid behavioral noise; the remaining correct trials with reaction time ranging .15–10 s were included in the analysis. IIVRT composite scores were computed as follows: (1) a ratio of the standard deviation (SD) to the mean reaction time was calculated for each task; (2) a natural log-transformation was performed for each ratio; (3) IIVRT score was derived by averaging the log-transformed ratios across the two tasks. Therefore, Greater IIVRT indicates larger inter-trial fluctuations and worse cognitive performance.

2.4. Imaging data acquisition

The fMRI data were collected at the Rochester Center for Brain Imaging using a 3T Siemens TrioTIM scanner (Erlangen, Germany) equipped with a 32-channel receive-only head and body coil transmission. The baseline 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), which provides high-resolution structure images for registration during preprocessing. The rs-fMRI data were collected using a gradient echo-planar imaging (EPI) sequence (TR/TE = 3000 ms/30 ms, FA = 90, slice thickness = 4 mm, matrix = 64 × 64, 4 × 4 mm in-plane resolution, 30 axial slices, volumes = 100) at both scans. Participants were asked to relax, keep their eyes open, and be awake during the entire scan.

2.5. Functional imaging data preprocess

The rs-fMRI data were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSFA) (Yan and Zang, 2010) based on SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). For each participant, the first 5 volumes of each rs-fMRI scan were excluded due to the noise related to the equilibrium of the scanner and the adaptation of the participants to the scanner. The remaining 95 volumes were slice timing and head-motion corrected, coregistered to their own structure image, and normalized to Montreal Neurological Institute (MNI) standard space, resampling (3 × 3 × 3 mm). After that, all of the data were smoothed using Gaussian kernel (FWHM 4 mm). After removing the linear trend, data were filtered using band pass (.01–.08 Hz) for functional connectivity (FC) analysis. Before calculating FC, nuisance covariates were regressed out, including 6 head motion parameters, global mean signal, white matter signal, and cerebrospinal fluid signal to reduce head motion effects and non-neuronal noise (Fox et al., 2006; Kelly et al., 2008).

2.6. Amygdala functional connectivity analysis

We selected the left and right amygdala as the seeds by using Automated Anatomical Labeling (AAL) templates (Tzourio-Mazoyer et al., 2002). The averaged fMRI time courses in left and right amygdala were used to generate whole brain FC, separately. Individuals' correlation coefficient map was Fisher's r-to-z converted at first. To examine the correlations between baseline amygdala FC and LOC, linear regressions were applied for internal and external LOC, separately. The correlation maps were then generated with a threshold of $p < .05$ using AlphaSim correction. Since only using smooth kernels in preprocessing is not sufficient, the effective smoothness for AlphaSim correction was estimated based on 4D residuals using DPABI_V2.3 toolbox (Yan et al., 2016). Using the toolkit to estimate the smoothness of the correlation maps, the estimated smoothness was (8.4, 7.8, 6.8) for internal LOC and (7.8, 7.4, 6.5) for external LOC, respectively. All the statistical maps were corrected for multiple comparisons at $p < .05$ by combining individual $p < .005$ with cluster size > 46 voxels, determined by Monte Carlo simulations (Ledberg et al., 1998). After the amygdala FC related to LOC were identified, the surviving brain regions were applied as masks. The averaged Z-transformed FC within each mask was extracted for baseline and post-task respectively, and their discrepancy was defined as the change of FC.

2.7. Other data analysis

SPSS 22.0 was used for data analysis. Group comparisons on sample characteristics were conducted using independent *t*-test for continuous variables or χ^2 tests for categorical variables. After extracting mean FC for both baseline and change, independent *t*-test was applied to examine the group difference. Generalized Linear Models (GLM) with an identity link and normal distribution were used to examine the interaction effect of group and FC on each LOC ($Y = \beta_0 + \beta_1 \times FC + \beta_2 \times Group + \beta_{interact}$ $FC \times Group$). P values from two-tailed tests less than .05 were subjected to the False Discovery Rate (FDR) to control for multiple comparisons among FC (meaning multiple FCs identified from the same domain of LOC at the same status). Mediation models were then estimated to test whether LOC mediated the effect of the FC (baseline or change) on cognitive performance. Bootstrapping of standard errors (5000 bootstrap draws) was used for indirect effect estimates using the INDIRECT macro from SPSS (Preacher and Hayes, 2008).

2.8. The effects of head motion

Some studies reported the confounding effect of head motion on resting-state FC (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012). Here we did not find any significant group difference in head motion indices (mean translation or rotation) for pre- or post-task scans (all $p > .08$). Regardless, we still conducted supplemental analyses controlling head motion indices when comparing group difference in LOC related FC.

3. Results

3.1. LOC and cognitive performance

The MCI group had significantly lower scores on the internal, but higher scores on the external LOC than did the HC group. The MCI group also showed significantly higher IIVRT than the HC group (see Table 1).

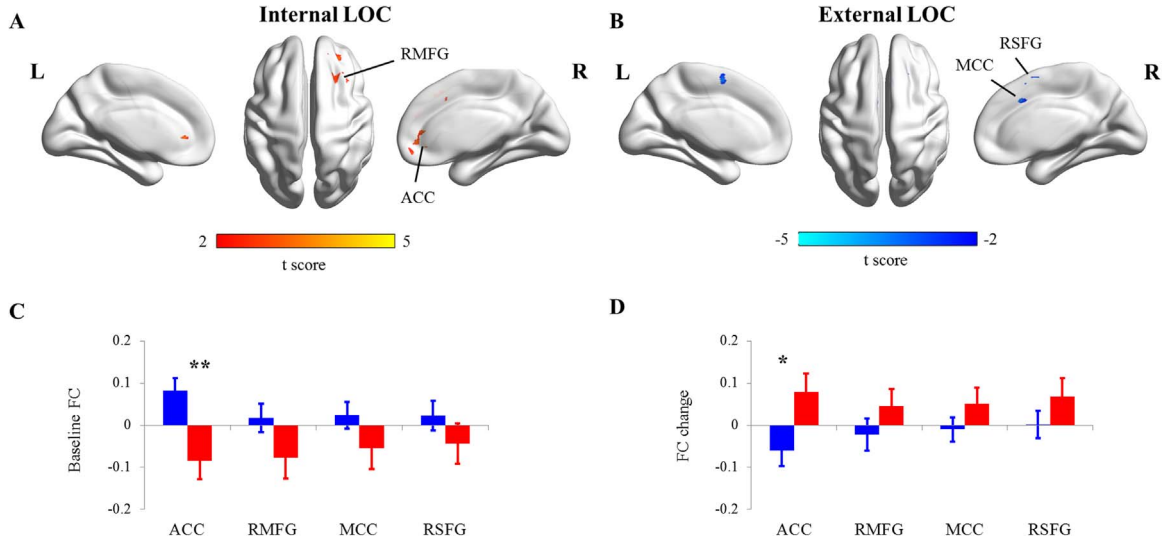

Fig. 1. LOC related amygdala networks. **A)** Univariate regression analysis was applied to examine the association between LOC and change of Ramygdala FC in the entire sample. Regions with individual $p < .005$ and number of cluster > 1188 mm^3 (corrected with AlphaSim at $p < .05$) were considered significant. Two regions, ACC and RMFG were found positively correlated with internal LOC. **B)** Applying the same regression analysis, two regions, MCC and RSFG were negatively correlated with external LOC. **C)** Comparisons of baseline Ramygdala involved FC between HC and MCI group. **D)** Comparisons of change of Ramygdala involved FC between HC and MCI group. Note. ACC, anterior cingulate cortex; RMFG, right medial frontal gyrus; RSFG, right superior frontal gyrus; MCC, middle cingulate cortex; LOC, locus of control; Ramygdala, right amygdala). Note. * group different $p < .05$; ** $p < .01$.

3.2. Associations between amygdala connectivity and LOC

Applying Pearson's correlation to examine the relationship between the amygdala networks with LOC (AlphaSim corrected $p < .05$), connectivity of right (R) amygdala with the anterior cingulate cortex (ACC) (MNI coordinate: −6, 36, 3; t = 4.71; cluster size = 93 voxels) and right middle frontal gyrus (RMFG) (MNI coordinate: 21, 18, 42; t = 4.41; cluster size = 256 voxels) were correlated with internal LOC (see Fig. 1A). Connectivity of Ramygdala with the middle cingulate cortex (MCC) (MNI coordinate: 6, 21, 36; t = 4.70; cluster size = 76 voxels) and right superior frontal gyrus (RSFG) (MNI coordinate: 9, 6, 60; t = 4.73; cluster size = 47 voxels) were correlated with external LOC (see Fig. 1B). Of note, one region located in the brain stem (MNI: −9, −45, −48, cluster size = 75 voxels) correlated with external LOC. Given our interest in the cerebrum, this region was excluded in the following analysis. Furthermore, controlling for head motion indices did not affect the results of FC. There were no significant associations between FC and LOC when taking left amygdala as the seed.

When comparing baseline and change of FC between groups, the MCI group had significantly lower baseline Ramygdala-ACC FC (t = 3.17, df = 38, p = .003) and greater increase in R-amygdala-ACC FC (t = −2.39, df = 38, p = .022) compared to HC group. There was no group difference at baseline or in change in other aspects of FC (see Fig. 1C). Of note, controlling for head motion indices did not affect the significance ($p < .05$) of these results.

Compared to the HCs, the MCI group had significantly stronger positive associations between internal LOC and two FCs, including baseline Ramygdala-ACC and Ramygdala-RMFG (see Table 2 and Fig. 2A), and stronger negative associations between internal LOC and change of these two FCs as well (Fig. 2C). There was no group by FC interaction effect on external LOC (Fig. 2B for baseline FC and Fig. 2D for change of FC).

3.3. Associations between amygdala connectivity, LOC and cognitive performance

For the entire sample, higher cognitive performance (lower IIVRT) was significantly related to higher baseline R-amygdala-RMFG (r = −.34, p = .035) and R-amygdala-MCC (r = −.37, p = .022), and smaller increase of R-amygdala-RMFG (r = .44, p = .005), R-amygdala-RFSG (r = .32, p = .047), and R-amygdala-MCC (r = .51, p = .001).

Table 2
GLM analysis of group and neural function (seeded in bilateral amygdala) on LOC.

	Group[a] × FC ($\beta_{interact}$)	
	B (SE)	Wald χ^2 (p)
Internal LOC		
ACC baseline	−2.84 (1.05)	7.23 (.007) [#]
ACC change	2.25 (1.04)	4.71 (.030) [#]
RSFG baseline	−2.43 (.87)	7.84 (.005) [#]
RSFG change	.98 (.47)	4.38 (.036) [#]
External LOC		
MCC baseline	−1.83 (.80)	.81 (.37)
MCC change	.50 (1.01)	.25 (.62)
RSFG# baseline	−.99 (.95)	1.09 (.30)
RSFG# change	−.54 (1.08)	.25 (.62)

Note. $Y = \beta \times FC + \beta \times Group + \beta_{interact}$ FC × Group; [a]taking HC as the reference; [#]Significant level after FDR correction for multiple comparisons. ACC, anterior cingulate cortex; RSFG, right superior frontal gyrus; MCC, middle cingulate cortex; LOC, locus of control.

For the entire sample, controlling for age, education, and MOCA, external LOC mediated the relationship between baseline Ramygdala-MCC FC (B (SE) = −.07 (.04), 95%CI: −.15, −.01), or baseline Ramygdala-RSFG FC (B (SE) = −.09 (.05), 95%CI: −.23, −.03), and cognitive performance. Controlling for age, education, MOCA and relevant baseline FC, external LOC also mediated the relationship between change of Ramygdala-MCC FC (B (SE) = .05 (.04), 95%CI: .0003, .15) and cognitive performance (see Fig. 3). There was no mediating effect of internal LOC. Given the small sample size, we did not separate the groups for the mediation analysis.

4. Discussion

In the current study, we investigated the relationships of amygdala networks with internal vs. external LOC between two cognitively distinct groups of older persons. We found significantly lower internal LOC but higher external LOC in the MCI group than the HC group. In the MCI group internal LOC showed a positive association with baseline FC of Ramygdala-ACC and Ramygdala-RMFG, and a negative association with FC changes of Ramygdala-ACC and Ramygdala-RMFG. HCs did not evidence these associations to the same extent as participants

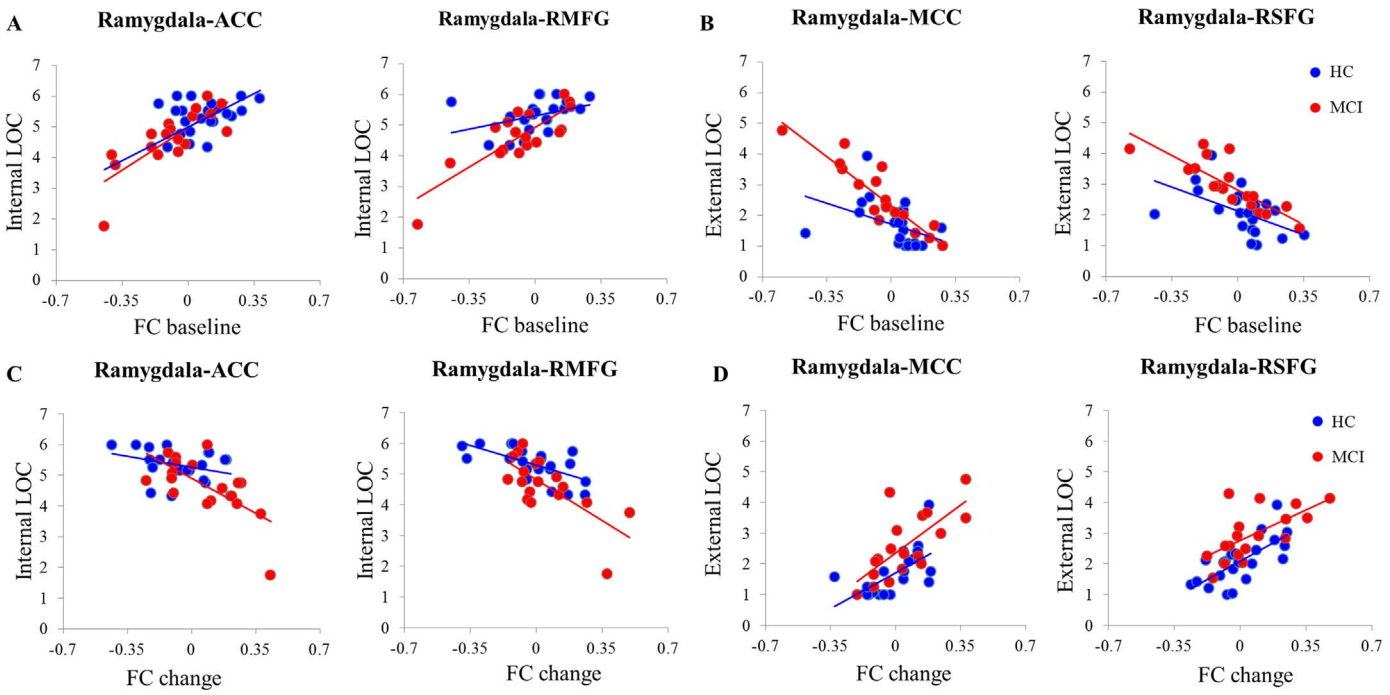

Fig. 2. Between-group comparison of the relationships between internal LOC and baseline amygdala networks **(A)**, external LOC and baseline amygdala networks **(B)**, internal LOC and change of amygdala networks **(C)**, and external LOC and change of amygdala networks **(D)**. Note. FC, functional connectivity; LOC, locus of control; ACC, anterior cingulate cortex; RMFG, right medial frontal gyrus; RSFG, right superior frontal gyrus; MCC, middle cingulate cortex; Ramygdala, right amygdala.

with MCI. Lending further support for the role of LOC in cognitive function and FC links, we found external LOC mediated the relationship between cognitive performance and FC of Ramygdala-MCC, as well as Ramygdala-RSFG for the entire sample.

Understanding LOC in cognitively impaired older adults, such as those with amnestic MCI, is a relatively new area. No study has examined external LOC, while only one emerging study compared the level of internal LOC between HC and MCI (Trivedi et al., 2016). Similar to our finding, Trivedi et al. (2016) found that the MCI group had significantly lower internal LOC compared to HC. In addition, there are two lines of indirect evidence providing support for a possible relationship between LOC and functional neural abnormalities observed in those with cognitive impairment. First, healthy aging literature has shown that cognitive performance has a positive relationship with internal LOC and a negative relationship with external LOC (Lachman and Andreoletti, 2006; Zahodne et al., 2015). To the extent that similar patterns of FC underlie cognitive performance in non-demented persons, but manifest in a more drastic or exaggerated way in amnestic

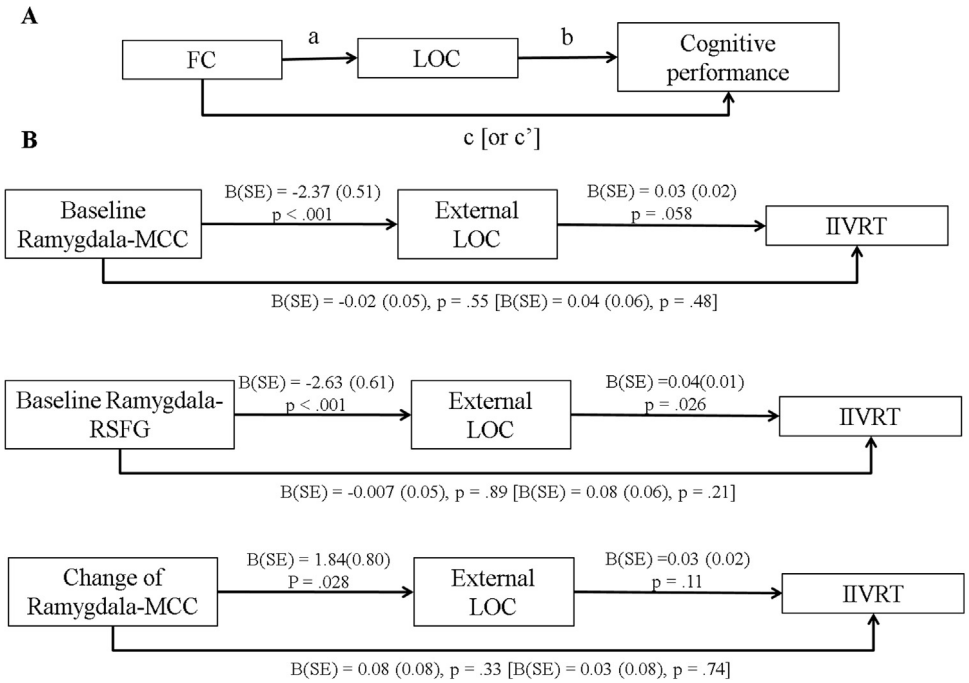

Fig. 3. Mediation models taking internal or external LOC as the mediator for the relationship between amygdala networks and cognitive performance. **A)** Conceptual model; **B)** External LOC mediates the association between amygdala networks at baseline or change and cognitive performance. Note. FC, functional connectivity; LOC, locus of control; RSFG, right superior frontal gyrus; MCC, middle cingulate cortex; Ramygdala, right amygdala; IIVRT, intra-individual variability in reaction time.

MCI, this evidence would then suggest that LOC as a marker of FC patterns to likely undergo significant alteration in disease states. The other indirect converging line of evidence relies on the two personality domains that are similar to LOC – neuroticism (similar to external LOC) vs. conscientiousness (similar to internal LOC). Current literature suggests higher neuroticism and lower conscientiousness predict the incidence of dementia and decline in memory function (Caselli et al., 2016; Duberstein et al., 2011; Low et al., 2013; Ramakers et al., 2015). Thus, LOC and/or similar traits may serve as phenotypic manifestations of either the function or vulnerability to abnormal brain alterations.

To the best of our knowledge, the present study is among one of the first studies examining the neural correlates of LOC in the context of cognitive impairment that is potentially AD related. Taking the amygdala as a seed, given its role in personality and cognition, we found different connections supporting internal vs. external LOC that were both located in the cingulate cortex and prefrontal cortex (PFC). The impaired integrity of functional and structural connectivity of both amygdala-PFC and amygdala-ACC pathways have been correlated with neuroticism (Haas et al., 2007; Madsen et al., 2016; McIntosh et al., 2013; Xu and Potenza, 2012). In addition, disruption of amygdala-PFC connectivity is related to trait anxiety (Kim and Whalen, 2009). Disruptions of amygdala-ACC or MCC connectivity are known to affect emotion regulation (Etkin et al., 2010; Pereira et al., 2010), and psychiatric disorders such as bipolar (Wang et al., 2009) and borderline personality (Cullen et al., 2011). Negative affect, a unifying characteristic of these disorders, is highly correlated to LOC (Lachman, 2006). Of note, only right amygdala connectivity was found to be associated with LOC in the present study. This is consistent with previous studies which reported that only the right amygdala was involved in anxiety and borderline personality disorders (Minzenberg et al., 2007; Phan et al., 2006). However, the lateralized effects of amygdala connectivity require further replication, considering the smaller sample size in the current study. Furthermore, we averaged the signal within an ROI to estimate its FC with the amygdala, neglecting the fact that heterogeneous functions may exist in certain ROI. The relationship between LOC and these functionally heterogeneous subregions may be further examined in the future.

For the group comparison of LOC-related amygdala connections, we found significant group differences in baseline and change of FC in ACC. For MCI group, the decreased baseline FC was in line with observed weak frontal-amygdala connections in AD associated degeneration in previous study (Yao et al., 2013). Meanwhile, enhanced FC in ACC immediately after the cognitive challenges in the MCI group was also observed previously when acute stress response was induced (van Marle et al., 2010). These findings indicate that the MCI group in general may have more stress reactivity from the cognitive challenges due to the dysfunctional cognitive and emotional regulatory circuit at rest. Furthermore, the finding of stronger relationships between amygdala connections and internal LOC in MCI group than HC suggests that personal control perceptions may be more strongly linked to fronto-amygdala circuits when cognitive function is compromised, as seen in MCI. Specifically, cognitively impaired individuals who perceive personal control over their cognitive function appear to show greater baseline fronto-amygdala connections (Goldberg et al., 2006). When faced with a cognitive challenge, these individuals show fewer increases in these connections, possibly because they are already active and more alike to the controls.

It may also be worthwhile to discuss the different sensitivity of these neural correlates to the type of LOC. One of the internal LOC related networks, amygdala-ACC FC, differed between MCI and HC groups both at baseline and in response to a cognitive task. Furthermore, the associations of internal LOC with amygdala-ACC and amygdala-RMFG FC, both at baseline and change, also significantly differed between groups. However, there was no group difference in external LOC-related neural correlates. Such differences in internal vs. external LOC-associated neural correlates need to be further validated in a larger sample size or prospective design. However, it is possible that MCI patients may be more sensitive to the consequence of subtle neural changes, such as deficits in daily cognitive performance. Such a process may affect how MCI patients perceive their own capacity, or internal LOC, more than perceptions that other forces outside them shape their cognitive competence (external LOC). A recent cognitive training, particularly relevant to executive function, has been effective in modifying internal but not external LOC (Wolinsky et al., 2010), while such training has been shown to modify PFC among MCI patients (Lin et al., 2016). This may provide a new therapeutic target for modifying cognitive decline in aging.

IIVRT measures the behavioral variability in cognitive tasks, and is considering as a reliable indicator for cognitive performance (MacDonald et al., 2006). Consistent with the literature (Hultsch et al., 2000), the MCI group tended to have higher IIVRT than HC group. Furthermore, IIVRT from the executive function tasks was associated with both internal and external LOC relevant neural subtracts, at both baseline and change. Most importantly, external LOC mediated the associations between amygdala connectivity (Ramygdala-MCC and Ramygdala-RSFG) and IIVRT for the entire sample. One imaging study reported that individuals with low internal LOC showed significant age-related cognitive decline and global brain volume decline in older adults (Pruessner et al., 2005a). Most imaging studies have focused on the role of personality in linking brain function with various outcomes. For example, extraversion mediates the relationship between left DLPFC volume and social well-being (Kong et al., 2015). Harm avoidance, another personality variable, modulates amygdala activity in response to attention tasks (Most et al., 2006). Our results indicated that external LOC might share the neural substrates with executive function regardless of cognitive impairment. Moreover, along with findings on the sensitivity of internal LOC-relevant neural subtracts to AD-associated neurodegeneration, it suggests potential dissociated roles of internal vs. external LOC in general cognitive aging vs. neurodegeneration.

Several limitations should be acknowledged. First, we only chose the amygdala as the seed based on previous studies. Other regions, such as insula (Stein et al., 2007), hippocampus (Pruessner et al., 2005b), medial PFC (Leotti et al., 2010), that are associated with personality traits or emotion regulation should be examined in the context of LOC. Second, due to the small sample size, we did not separate the mediation model by group (but we did control for global cognition). Whether LOC links to neural subtracts and cognitive performance differently given the clinical status needs to be further investigated. Relevantly, we did not control for memantine/cholinesterase inhibitor use due to the small number of users (n = 3). However, these medications may affect the neural activities in amygdala in previous animal models (Reus et al., 2012); hence, a relevant investigation with a large sample size is needed. Third, given the main purpose of assessing the neural subtracts of LOC, we contrasted the rs-fMRI derived brain networks before and after cognitive challenge task protocol. The cognitive task-related fMRI may provide an alternative aspect in terms of understanding whether LOC links to any executive function relevant neural subtracts. This may be particularly important for LOC in the context of cognitive control. Fourth, we suspected internal LOC might be more relevant to AD-associated neurodegeneration than external LOC. This assumption was simply based on the diagnostic classification seen in MCI, which needs to be further tested directly with AD pathology data. Finally, we utilized substantial neural evidence from two personality traits (conscientiousness and neuroticism) assuming the similarity between LOC and these personality traits. However, the neural subtracts underlying personality vs. LOC, especially in relation to AD, need to be further studied to develop effective therapeutic strategies in modifying AD-associated neurodegeneration.

5. Conclusions

Our study differentiated the neural substrates underlying internal vs. external LOC, and their role in cognitive performance by comparing normal aging with amnestic MCI. The results suggested that the function of amygdala, by linking to the cingulate cortex and PFC, may be critical in understanding the role of LOC in cognitive performance in the context of cognitive aging.

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