Acute Affective Reactivity and Quality of Life in Older Adults with Amnestic Mild Cognitive Impairment: A Functional MRI Study

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Objectives: Poor quality of life (QoL) is a major concern among older adults with amnestic mild cognitive impairment (MCI). Maladaptive affective regulation and its relevant frontal dysfunction that are often observed in older adults with MCI may provide an insight into the understanding of their QoL. Methods: In this case-controlled study, participants (MCI patients, N = 18; healthy comparisons [HC], N = 21) completed cognitive tasks, and underwent resting-state functional magnetic resonance imaging (rs-fMRI) immediately before and after the tasks. The amplitude of low-frequency fluctuations (ALFF) of rs-fMRI signals was calculated to examine the brain’s spontaneous activity. The change in valence from the Self-Assessment Manikin indexed affective reactivity. QoL was assessed using Quality of Life-AD measure. Multiple mediator model was used to examine the mediating effect of frontal regions’ ALFF reactivity between the affective reactivity and QoL. Results: The MCI group had significantly worse QoL and more negative affective reactivity than HC group. Less negative affective reactivity was significantly associated with better QoL in MCI not HC. ALFF in the anterior cingulate cortex, medial prefrontal cortex (MPFC), and superior frontal gyrus (SFG) increased significantly less after cognitive tasks in MCI than HC. For the entire sample, greater increases of ALFF in MPFC and SFG were significantly associated with better QoL, and SFG alone significantly mediated the association between affective reactivity and QoL. Conclusions: Enhancing SFG activation, especially among those with MCI, may provide a therapeutic target for addressing the negative impact of maladaptive affective regulation on QoL. (Am J Geriatr Psychiatry 2017; ■■■•■•–■■)

Key Words: Quality of life, affective reactivity, low-frequency fluctuation, prefrontal cortex, mild cognitive impairment, resting-state fMRI

Article Highlights
• Mild cognitive impairment patients had diminished QoL.
• Prefrontal cortex’s reactivity to cognitive challenge related to QoL.
• Prefrontal cortex’s reactivity linked negative affective reactivity with QoL.

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Quality of Life in MCI

Q uality of life (QoL) is a subjective and multidimensional concept, encompassing physical, psychological, and social aspects and reflecting well-being and life satisfaction in an individual’s daily life. Cumulative studies indicate that, compared with their cognitively healthy counterparts, lower QoL is a major concern among older adults with Alzheimer disease (AD), and its symptomatic preclinical stage, amnestic mild cognitive impairment (MCI). To improve QoL in these older adults, it is critical to understand factors contributing to QoL and the relevant neural basis.

Maladaptive stress regulation, especially the affective component, often contributes to poor QoL. For example, a review study of stress and intervention reported a close relationship between affective regulation and social well-being. On the other hand, even subtle age-related declines in cognition can compromise older adults’ engagement of adaptive affective regulation strategies, especially in response to tasks with cognitive challenges. Therefore, examining the affective response to cognitive challenges (i.e., affective reactivity) may provide insight into the understanding of poor QoL in older adults with cognitive impairment.

Magnetic resonance imaging (MRI) can contribute to the understanding of individual differences in affective reactivity and QoL, and/or the link between them. Previous studies found that lower QoL was associated with more severe white matter hyperintensities across the whole brain, thinner cortical thickness of specific regions such as the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), and disrupted regional homogeneity within the ACC. Meanwhile, the functions of ACC and PFC link to stress regulation, including the affective reactivity, as well as individuals’ performance in cognitive challenges. Under the circumstance of stressful life events, a normal brain would determine what is stressful, regulate the physiological, mental, and behavioral responses to cope with the stressors, and revise the plasticity of the brain adaptively as a consequence of physiological coping with the stressors. To the best of our knowledge, however, no study has directly explored the neural relevance of stress regulation and its association with QoL among individuals at a risk for AD.

Here we applied amplitude of low-frequency fluctuations (ALFF) of resting-state functional MRI (rs-fMRI) signal, which measures the total power of blood oxygen level dependent (BOLD) time course within a specific frequency range (typically 0.01–0.08 Hz) to examine the brain’s spontaneous activities. ALFF has been identified as a sensitive marker in predicting AD-related neurodegeneration. Resting-state hyperactivation (indexed by high ALFF) in the frontal regions has been reported in older adults with cognitive impairment (including MCI) compared with their cognitively healthy counterparts, which may act as a way to compensate for its low neural efficiency. Whether the frontal activities in response to cognitive challenges would explain the relationship between disrupted acute affective reactivity to such challenges and compromised QoL, however, has not been examined.

In the current study, we examined: 1) the difference in acute affective reactivity (indexed by the change in valence) to cognitive challenges and QoL between amnestic MCI and healthy comparisons (HC); 2) the relationship between acute affective reactivity and QoL; and 3) the neural correlates linking the association between acute affective reactivity and QoL. We hypothesized that negative affective reactivity to cognitive challenges may compromise QoL via the abnormalities of frontal reactivity in response to cognitive challenges in old age.

METHODS

Participants

Thirty-nine participants (HC = 21, MCI = 18) completed the study. Participants with amnestic MCI were recruited from the university-affiliated memory clinics using the clinical diagnosis of “mild cognitive impairment due to Alzheimer disease”. All MCI group participants had deficits in memory based on a comprehensive neuropsychological battery, intact basic activities of daily living, intact or mild deficits in instrumental activities of daily living, and an absence of dementia using NINCDS-ADRDA criteria per assessments. Participants in this group using AD medication (i.e., memantine or cholinesterase inhibitors) had to be on a stable dose of their medication(s) for 3 months prior to enrollment. Healthy comparisons were recruited from the community (e.g., senior centers), had no self-reported history of dementia or MCI, and had intact global cognition and episodic memory abilities validated with their scores on the Montreal Cognitive Assessment (MoCA >25 if years of education >12, or MOCA >24 if years of education ≤12) and Rey’s Auditory Verbal
Learning Test (RAVLT > 6). In addition, participants from both groups were required to have the capacity to give consent (based on research teams’ assessment), adequate visual and auditory acuity for testing, be at least 60 years of age or older, English-speaking, and community-dwelling. Exclusion criteria included the presence of severe cardiovascular conditions (e.g., chronic heart failure), severe inflammatory disease (e.g., irritable bowel syndrome), severe uncontrollable psychiatric disorders (e.g., major depression), or MRI contraindications (e.g., pacemaker, claustrophobia). The study was approved by the University of Rochester’s research subject review board.

**Design and Procedure**

The present study used a laboratory-based experiment protocol, consisting of two sessions within a 2-week window. The first session entailed neuropsychological and behavioral interviews. The second session included an acute cognitive challenge protocol beginning in a 2-hour morning window (9–11 AM), to avoid potential diurnal fluctuation in cognitive and neurobiological functions. Participants were instructed to eat breakfast but avoid nicotine, caffeine, or exercise for at least 2 hours before arrival. In relation to the present study, the following phases were included in the protocol: acclimation/baseline (15 minutes), first MRI (30 minutes, assess T1 structure and baseline rs-fMRI), cognitive challenge tasks outside the MRI scanner (30 minutes), and second MRI (15 minutes, assess rs-fMRI). The cognitive challenge tasks included two commonly used computerized tasks: Stroop Word Color (focusing on inhibition) and Dual 1-Back task (focusing on working memory), each lasting 10 minutes. Participants practiced each task prior to scanning to become familiar with them. The order of the two tasks was randomized across participants.

**Measures**

QoL was assessed with Quality of Life-AD measure in the first session. This measure covers domains of QoL thought to be important in cognitively impaired individuals, such as relationships with friends and family, concerns about finances, physical condition, and mood. There are 13 items, each using a 4-point scale to measure QoL (1 = Poor to 4 = Excellent). Scores for each item are summed for a total QoL score ranging from 13 to 52, with higher scores indicating better QoL. The Cronbach’s α was 0.85 for the entire sample in the present study.

Affective reactivity to cognitive challenges was measured with self-reported valence rating from the self-assessment manikin (SAM) at baseline and immediately after the cognitive tasks in the second session. The SAM assesses affective status using a 5-point pictorial scale (with scores ranging from 1 to 5), in which higher scores indicate more positive affect. We also calculated affective reactivity by subtracting baseline scores from post-task scores, with higher discrepancy scores indicating less negative affective reactivity.

Cognitive performance in the cognitive challenge tasks was measured as an additional index to verify the actual meaning of the change of ALFF after cognitive tasks. If the changes of brain activation after cognitive tasks are merely due to the rs-fMRI data acquisition–related “regression to mean” phenomenon instead of reflecting the actual neural engagement in cognitive challenges, the change of ALFF should have no relationship with an individuals’ cognitive capacity. We used intra-individual variability in reaction time (IIVRT) from the cognitive tasks, which measures the within-person fluctuations across trials, to assess the cognitive task performance. Compared with mean reaction time or response accuracy, IIVRT is more valid in reflecting cognitive capability, including in neurodegenerative disorders. For each task (Stroop or 1-Back), the first three trials were excluded to avoid behavioral noise; and reaction times shorter than 150 msec or longer than 10 sec were excluded in the analysis as RTs outside the bounds likely reflect errors; the reaction times of the remaining trials with correct responses were used in calculating IIVRT. 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. Higher IIVRT indicates worse cognitive performance. The IIVRT ranged between 0.28 and 0.33 in HC group, and between 0.36 and 0.42 in MCI group.

**MRI Data Acquisition**

The fMRI data were collected at the Rochester Center for Brain Imaging using a research-dedicated 3T Siemens
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TrioTIM scanner (Erlangen, Germany) equipped with a 32-channel receive-only head and body coil transmission. In the baseline fMRI session, the scan began with a MPRAGE scan (TR/TE = 2,530/3.44 msec, TI = 1,100 msec, FA = 7, matrix = 256 × 256, resolution 1 × 1 × 1 mm3, slice thickness = 1 mm, 192 slices), which provides high-resolution structure images for registration in preprocessing. The rs-fMRI data were collected using a gradient echo-planar imaging (EPI) sequence (TR = 3,000 msec, TE = 30 msec, FA = 90, slice thickness = 4 mm, matrix = 64 × 64, 4 × 4 mm in-plane resolution, 30 axial slices, volumes = 100) at both baseline and post-task. Each rs-fMRI scan lasted for 5 minutes. Participants were required to keep their eyes open and stay awake during the entire scanning.

MRI Data Preprocessing and Analysis

The functional imaging data were preprocessed using the Data Processing Assistant for Resting-State fMRI (DPARSFA) based on SPM8 (http://www.fil.ion.ucl.ac.uk/spm/).27 For each individual, the first 10 volumes of each fMRI scan were excluded to avoid the noise related to the equilibrium of the scanner and to ensure the adaptation of the participants to the scanner. The remaining 90 volumes were preprocessed by correcting slice timing and head motion. Then the functional images were registered to the individual’s own structure image, and normalized to Montreal Neurological Institute (MNI) standard space. Because head motion might influence rs-fMRI data analysis, in addition to the preprocessing, we also visually examined each individual’s head movements and compared the two groups’ head motion in six parameters (3 translation and 3 rotation). There were no significant differences in any parameter for both baseline (all p > 0.4, corrected by false discovery rate [FDR]) and post-task (all p > 0.09, corrected by FDR). Therefore, head motion was not included in the following analysis. Lastly, all data were spatially smoothed using Gaussian kernel (FWHM = 4 mm). After removing the linear trend, data were filtered using band pass (0.01–0.08 Hz) to implement ALFF analysis. Briefly, the BOLD time series was converted to the frequency domain by using the fast Fourier transform. The square root of the power spectrum was then calculated, averaged across 0.01–0.08 Hz for each voxel, and defined as the ALFF at the given voxel.27

Based on whole brain voxel-based analysis, repeated-measures ANOVA was used to examine the interaction effects of group (HC versus MCI) × task status (baseline versus post-task) in ALFF in SPM8. A threshold of corrected p < 0.01 (uncorrected p < 0.01 and cluster >540 mm3) was used. The correction of multiple comparisons was applied within the whole brain mask and determined by Monte Carlo simulations using the AFNI AlphaSim program (https://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf).28 The ALFF value of individual voxels within each survived brain region was then averaged and extracted for the following analysis.

Other Data Analysis

Data analyses were conducted using SPSS 22.0. Group comparisons on sample characteristics, including QoL and baseline ALFF, were analyzed using independent t tests for continuous variables or χ2 tests for categorical variables. Repeated-measures ANOVA was used to examine the effect of task status (baseline versus post-task) on valence scores for both groups as preliminary analysis. Pearson’s correlation was applied to examine the relationship between affective and ALFF reactivity. Generalized linear models (GLMs) with an identity link and linear scale response were used to examine both the main effect of affective or ALFF reactivity (Y = βmain × Reactivity + ε) and the interaction effect of reactivity and group (Y = β × Reactivity + β × Group + βinteraction × Reactivity × Group) on QoL. The HC group was used as the reference group for determining the interaction effect with Wald’s test in the GLMs. All tests with a two-tailed p value less than 0.05 were considered significant. The FDR correction was applied to p values to control for multiple brain region comparisons.29

Multiple mediator model, estimated to test whether the ALFF reactivity of brain regions, both individually (individual regions) and jointly (summed effect of multiple regions), mediated the effect of the affective reactivity on QoL. We used the entire sample and controlled for age, sex, years of education, and MoCA score in the analysis. The INDIRECT macro from SPSS was used to conduct the multiple mediation analysis based on a multivariate extension of the product-of-coefficients approach.30 To estimate the indirect effect through ALFF reactivity, we applied 5,000 bootstrap samples to generate 95% confidence intervals (CIs) for the standardized indirect effect. If an empirical 95%
RESULTS

Sample Characteristics

The two groups were similar in their age, sex, and education. The MCI group had significantly lower scores for the MoCA and RAVLT than the HC group.

Group Comparison for QoL and Valence

The MCI group also had significantly lower scores on QoL measure (see Table 1). There was a significant decline in valence score after the cognitive tasks in the MCI group (F(1, 37) = 10.37, p = 0.005), but not the HC group (F(1, 37) = 2.50, p = 0.13) (see Figure 1A).

Group Comparison for ALFF Reactivity

Applying repeated-measures ANOVA in whole brain voxel-wise ALFF analysis, we identified significant interaction effect of group by task status in three brain regions: the ACC, medial PFC (MPFC), and superior frontal gyrus (SFG) (see Figure 1B). The MCI group had significantly higher baseline ALFF in all regions than HC (ACC: t(37) = 4.02, p < 0.001; MPFC: t(37) = 3.18, p = 0.003; SFG: t(37) = 3.63, p = 0.001). Controlling for baseline ALFF values, the HC group had a significantly greater increase in ALFF after task completion in all three regions (ACC: F(1, 37) = 6.60, p = 0.015; MPFC: F(1, 37) = 21.48, p < 0.001; SFG: F(1, 37) = 20.28, p < 0.001) than MCI.

Also, lower IIVRT, reflecting better cognitive performance, was significantly related to higher ALFF reactivity (i.e., greater increase in ALFF after cognitive

CI does not include zero, the indirect effect was significant at the p less than 0.05 level.
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Association between Valence and ALFF Reactivity

Higher valence reactivity (i.e., less negative affective reactivity) was correlated to higher ALFF reactivity in SFG \( r_{(37)} = 0.43, p = 0.007 \) but not other regions for the entire sample. There was no group effect in the relationship.

Associations of Valence or ALFF Reactivity with QoL

In terms of the main effect of valence or ALFF reactivity, higher QoL was significantly related to higher ALFF reactivity of the MPFC \( B (SE) = 12.64 (5.01) \), Wald \( \chi^2(1) = 6.37, p = 0.012 \) and SFG \( B (SE) = 14.44 (6.00) \), Wald \( \chi^2(1) = 5.79, p = 0.016 \) for the entire sample (Figure 2B). There was no main effect of valence reactivity on QoL. In terms of the interaction effect (i.e., reactivity by group), compared with HC group, there was a significantly greater positive association between valence reactivity and QoL in MCI \( B (SE) = 3.52 (1.56) \), Wald \( \chi^2(1) = 5.09, p = 0.024 \) (see Figure 2A). There was no interaction effect of ALFF reactivity by group on QoL. In addition, valence and the three regions’ ALFF reactivity at baseline was not related to QoL in the main or interaction effect analyses (all \( p > 0.05 \)).

Mediation Models of ALFF Reactivity on the Association between Valence Reactivity and QoL

Because a significant correlation between ALFF reactivity and QoL was observed for the entire sample, instead of individual groups, the primary mediation analysis was conducted for the entire sample. Controlling for age, sex, years of education, and MoCA score, ALFF reactivity in the SFG significantly mediated the association between valence reactivity and QoL (standardized indirect effect: beta = 0.14, SE = 0.09, 95% CI: 0.01–0.37) (see Figure 3). ALFF in other brain regions, or combination of regions, did not mediate the association between valence reactivity and QoL.

When analyzing the mediation models by group, the mediating effect (indexed by standardized indirect effect) was not significant (MCI: beta = 0.01, SE = 0.16, 95% CI: −0.39 to 0.25; HC: beta = 0.03, SE = 0.09, 95% CI: −0.08 to 0.27).

DISCUSSION

The present study investigated the neural correlates of the association between acute affective reactivity to the cognitive tasks and perceived QoL in older adults at high risk for AD. Compared with HC, MCI participants had significantly more negative affective response to cognitive challenges and showed a significant lower perceived QoL. Furthermore, in MCI patients, less...
negative affective reactivity to the cognitive tasks was associated with better QoL, but this association was not found in HC. Baseline ALFF in ACC, MPFC, and SFG was significantly lower in HC, whereas increases of ALFF after the cognitive tasks in these regions were significantly greater in the HC group. Along with the findings in ALFF changes, better cognitive performance was also related to a greater increase of ALFF in all three regions. For the entire sample, greater increases of ALFF in the MPFC and the SFG were associated with better QoL, and this increase of ALFF in the SFG was also associated with less negative affective reactivity. Further mediation analysis revealed that reactivity of ALFF in the SFG mediated the association between affective response and QoL in all participants. The study was underpowered to detect significant mediation effect within individual groups, however.

Cumulative literature suggests patients with AD or MCI have compromised QoL. Factors, such as neuropsychiatric symptoms, functional deficits in daily living, and compromised mental health, contribute to their poor QoL. Studies of stress regulation, of which affective reactivity to challenging environment is a critical component, underscore the potential integrative role of stress regulation in understanding QoL. For instance, evidence suggests maladaptive stress regulation can affect life satisfaction. Additionally, individuals with neuroticism, who are more physiologically and emotionally reactive to stressors, tend to experience poorer QoL. In the present study, we examined affective reactivity, as indexed by change of valence, in the context of cognitive challenge. This can be particularly meaningful for older adults at high risk for AD or cognitive decline, who frequently experience negative emotions, such as anger or anxiety, in response to the failures or challenges of cognitive tasks in their daily lives. The consequences of this affective response have not been emphasized, however. Consistent with our hypothesis, more negative affect after the cognitive tasks appeared among participants from the MCI group, and QoL was more tied to negative affect change in the MCI group as well. Of note, here we used Stroop Word Color Task and dual 1-Back task with cognitive demands on inhibition and working memory to simulate the cognitive stressors older adults often encounter in their daily lives. These tasks and other cognitive challenges have been commonly used to induce stress response, including affective reactivity.

It is well known that PFC and ACC play crucial roles in many high level functions, including executive functions and emotion modulation, while their functions are compromised early in the AD-associated neurodegenerative process. A morphometry study found negative relationships between QoL and regional gray matter volume in left PFC and dorsal ACC. In the present study, we did not find an association between QoL and brain function at baseline; instead, greater reactivity of MPFC and SFG after cognitive tasks was associated with better QoL in older adults with and without MCI. Of note, although the ALFF of ACC, MPFC, and SFG increased significantly more in the HC group than the MCI group, these regions’ ALFF were significantly higher in MCI group at baseline. Such brain functional difference at baseline and in response to cognitive tasks may indicate dysfunctional compensatory effect of PFC that fails to modulate cognitive tasks in MCI. That is, the MCI group tends to have higher spontaneous activity in the frontal regions than the HC group at rest, which helps compensate for the disconnection of the posterior brain regions and maintain physiological function chronically. In response to acute cognitive tasks as seen in the present study, however, frontal regions of the MCI group may have lost the capacity to function immediately.
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Lastly, we found that greater increase of ALFF in SFG to cognitive tasks mediated the association between less negative affective reactivity and better QoL. Cumulative literature suggests maladaptive stress regulation leads to brain plastic changes, especially in frontal regions.\textsuperscript{16} Such frontal dysfunction may cumulatively lead to compromised QoL. Interventions targeting SFG may be beneficial for improving QoL. Notably, the task paradigms used as the cognitive stress task (e.g., working memory task and inhibition task) that linked to SFG, have been be used as components of cognitive training.\textsuperscript{45,46} Likewise, targeting emotion regulation (e.g., mindfulness\textsuperscript{47}) could impact SFG in ways that benefit QoL. Nevertheless, a relevant limitation is that a causal relationship between affective reactivity, SFG reactivity, and QoL cannot be determined with the current design with statistical mediation effect. Also, the current mediating effect from SFG may only account for a small proportion of the relationship between affective reactivity and QoL. Clarifying the causal pathway, ideally in a relatively large sample size, will be necessary to validate the effect size of the mediator, especially within individual groups, which will help further understand the mechanistic difference in QoL and develop effective clinical interventions.

An additional limitation relates to our measure of affect. We only applied the SAM valence subscale to assess affective response to cognitive challenge as a marker of affective reactivity. A more comprehensive measure of both positive and negative affect (e.g., anxiety), and the capacity for their regulation, may help clarify the role of affective response in QoL.

CONCLUSIONS

Compared with cognitively healthy older adults, individuals with amnestic MCI tended to have poorer QoL, which was more sensitive to the negative affect arising from cognitive challenges. The PFC’s reactivity to cognitive challenges, especially in the SFG, may reveal the neural correlates for the relationship between affective reactivity and QoL.

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