Altered sulcogyral patterns of orbitofrontal cortex in patients with mild cognitive impairment

Zixiang Wang\textsuperscript{a,\textcopyright,\#}, Xin Zhang\textsuperscript{b,\#}, Renyuan Liu\textsuperscript{b}, Yang Wang\textsuperscript{b}, Zhao Qing\textsuperscript{b,c}, Jiaming Lu\textsuperscript{b}, Ignacio Obeso\textsuperscript{d}, Bing Zhang\textsuperscript{b,c,\ast}, Yansong Li\textsuperscript{a,c,\ast}\textsuperscript{\textcopyright}

\textsuperscript{a} Reward, Competition and Social Neuroscience Lab, Department of Psychology, School of Social and Behavioral Sciences, Nanjing University, Nanjing, China
\textsuperscript{b} Department of Radiology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China
\textsuperscript{c} Institute for Brain Sciences, Nanjing University, Nanjing, China
\textsuperscript{d} HM Hospitales – HM CINAC, Móstoles, Universidad CEU-San Pablo, Madrid, Spain

\textbf{ARTICLE INFO}

\textbf{Keywords:}
Orbitofrontal cortex
Sulcogyral pattern, MCI
Magnetic Resonance Imaging

\textbf{ABSTRACT}

Mild cognitive impairment (MCI) is increasingly recognized as a risk factor for Alzheimer’s disease (AD). Neuroimaging studies have revealed structural abnormalities in the orbitofrontal cortex (OFC) in MCI patients, while other findings fail to report anatomical alterations. Accordingly, structural changes in this brain region amongst MCI patients has not been well characterized. Given that OFC sulcogyral organization has increasingly been demonstrated as a reliable pre-morbid marker of pathological conditions in several neuropsychiatric disorders, we examined the distribution of OFC sulcogyral patterns (classified into Type I, II and III) based on structural brain data from 68 MCI patients and 55 healthy controls. Our results, supported by both Frequentist and Bayesian statistics, showed that MCI patients exhibited an increased prevalence of Type II pattern compared with healthy controls, particularly in the right hemisphere. Meanwhile, MCI patients showed a decreased prevalence of Type I pattern compared with healthy controls. Taken together, our results reveal a skewed distribution of OFC sulcogyral in MCI patients, possibly reflecting a potential neurodevelopmental risk marker of MCI.

1. Introduction

Mild cognitive impairment (MCI) is the intermediate stage between the cognitive decline of normal aging and dementia, which involves cognitive deficits greater than expected for their age (DeCarli, 2003; Gauthier et al., 2006; Petersen and Negash, 2008; Silverberg et al., 2011; Traykov et al., 2007; Tzivian et al., 2016; Zamarian et al., 2010). In line with the idea that neuropsychiatric disorders have a biological basis in the brain (Insel et al., 2010), functional neuroimaging studies have revealed a core network of dysfunctional brain regions in patients with MCI, including the orbitofrontal cortex (OFC) (Fan et al., 2008; Schroeter et al., 2009; Wee et al., 2013). Hypoactivity in the OFC has been observed across a number of cognitive tasks (Balardin et al., 2015; Drzezga et al., 2003). However, it remains unclear whether such functional alteration in the OFC underlies structural abnormalities in patients with MCI. Although an early study using magnetic resonance imaging (MRI) failed to report between-group differences in OFC gray matter volume (Chetelat et al., 2002), more recent studies reported reduced OFC gray matter volume (Bozzali et al., 2006; Hämäläinen et al., 2007; Han et al., 2011; Schroeter et al., 2009), cortical thinning (Seo et al., 2010; Singh et al., 2006) and decreased OFC volume (Driscoll et al., 2009) in patients with MCI compared with healthy controls. These mixed results might be caused by potentially confounding factors such as statistical power, comorbidities and head motion acting on structural brain measures (Madan, 2018). Moreover, given these studies focused on cortical volume and thickness as meaningful sources of structural deficits, it remains unclear whether such structural abnormalities in the OFC represent a premorbid development marker or rather a consequence of the disease, as discussed in other studies (Fusar-Poli et al., 2013; Lorenzetti et al., 2009). One possible way to address the underlying causes of OFC changes in MCI is to explore the OFC sulcogyral organization.

OFC sulcogyral organization has been demonstrated to be governed by the degree of cortical folding which occurs in early pregnancy and leads to stable sulcogyral patterns across the life span (Armstrong et al., 1995; White et al., 2010). The OFC sulcogyral organization measures...
have been demonstrated to be promising for yielding information about potential neurodevelopmental mechanisms in many neuropsychiatric conditions (Kelly et al., 2013; Kühn et al., 2016; White et al., 2003), possibly raising the hope that they may eventually be employed to more precisely identify the time of onset of neural abnormalities in elderly MCI patients. Moreover, these stable sulcogyral patterns provide sensitive and reliable measures of structural variability in the OFC, which are not dependent upon potentially confounding factors such as disease duration or medication use (Whittle et al., 2014). As a result, it is conceivable that such reliable structural traits provide a unique opportunity to examine putative premorbid markers of MCI. OFC sulcogyral patterns can be classified into three main different types (Types I, II and III) based on the continuity/discontinuity of the medial and lateral orbitofrontal sulci (Chiavaras and Petrides, 2000).

In previous studies, alterations in OFC sulcogyral patterns have been well characterized in the context of schizophrenia. Nakamura et al. (2007) initially revealed a decreased proportion of Type I pattern and an increased proportion of Type II and Type III patterns in patients with schizophrenia. These findings have been further replicated in more recent studies (Bartholomeusz et al., 2013; Copley et al., 2015; Isomura et al., 2017; Nishikawa et al., 2016; Takayanagi et al., 2010; Uehara-Aoyama et al., 2011). Moreover, such observations can even be extended to individuals at increased risk for developing schizophrenia (Chakirova et al., 2010; Lavioie et al., 2014; Nakamura et al., 2018; Takahashi et al., 2019), suggesting that Types II and III might represent premorbid structural markers of schizophrenia. In addition, researchers have recently attempted to characterize alterations in OFC sulcogyral patterns in patients outside of schizophrenia. Two recent studies reported an increased prevalence of Type III in autism spectrum disorders (Watanabe et al., 2014) and an increased prevalence of Type II in pathological gamblers/gambling disorders (Li et al., 2019) respectively, while another study further showed that Type III was related to greater lifetime cannabis consumption in cannabis users (Chye et al., 2017).

The above studies demonstrate that the associated changes in OFC sulcogyral patterns are reliable premorbid structural markers in neuropsychiatric disorders (Nakamura et al., 2020) and therefore may as well be important to characterize the structural abnormalities in patients with MCI. Based on these considerations, the current study aims to illustrate OFC sulcogyral patterns in patients with MCI and the relationship with cognitive functions, under the premise that the well-described anatomical impairments reported in the OFC might reflect pre-morbid structural markers. Because we found it hazardous to make any predictions based on the existing research literature, we refrained from making specific hypotheses and considered this study to be exploratory.

2. Methods

2.1. Participants

The procedure of recruiting participants was based on our prior studies (Ni et al., 2016; Qing et al., 2017; Zhao et al., 2015). In the present study, we included 68 patients with mild cognitive impairment (MCI) (38 men / 30 women, age = 68.62 ± 11.77 years; right-handed). All participants underwent neurologic and physical evaluations by a trained neurologist as well as standard neuropsychological assessment by two neuropsychologists, all of whom have expertise in the diagnosis of dementia and MCI. Moreover, participants underwent an MRI examination, as well as routine biologic screening, thus excluding non-neurodegenerative causes of cognitive decline. Participants were diagnosed with MCI according to the standard criteria (Petersen, 2004; Petersen et al., 2001). Consensus diagnoses were reached based on clinical interviews, medical chart reviews, questionnaires completed by participants, informant’s responses, neuropsychological data and structural MRI to exclude other disorders. All MCI participants had subjective memory complaints, supported by an informant, and showed a condition characterized by mild recent memory loss without dementia (test score, 1.5 SDs below age-adjusted norms). Additionally, participants had normal activities of daily living and a Clinical Dementia Rating (CDR) score of 0.5. Severity of cognitive impairment was assessed by the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and Mini-Mental State Examination (MMSE) (Folstein et al., 1975), which are the sole cognitive measures to classify individuals as cognitively normal or MCI. Meanwhile, based on medical records and information from family members and patients, the following exclusion criteria were used: 1) a history of stroke or transient ischemic attack (TIA); 2) neurological diseases (multiple sclerosis, AD, Parkinson’s disease); 3) a history of head trauma with more than 5-min loss of consciousness; 4) a current or past history of substance dependence; and 5) cardiovascular diseases (angina, hypertension, heart attack). We also recruited 55 healthy controls (HCs) (33 men / 22 women, age = 66.67 ± 10.65 years; right-handed) reporting no neuropsychiatric disorders (Nasreddine et al., 2005) and Mini-Mental State Examination (MMSE) (Folstein et al., 1975), which are the sole cognitive measures to classify individuals as cognitively normal or MCI. Meanwhile, based on medical records and information from family members and patients, the following exclusion criteria were used: 1) a history of stroke or transient ischemic attack (TIA); 2) neurological diseases (multiple sclerosis, AD, Parkinson’s disease); 3) a history of head trauma with more than 5-min loss of consciousness; 4) a current or past history of substance dependence; and 5) cardiovascular diseases (angina, hypertension, heart attack). We also recruited 55 healthy controls (HCs) (33 men / 22 women, age = 66.67 ± 10.65 years; right-handed) reporting no neuropsychiatric disorders (Nasreddine et al., 2005) and Mini-Mental State Examination (MMSE) (Folstein et al., 1975), which are the sole cognitive measures to classify individuals as cognitively normal or MCI. Meanwhile, based on medical records and information from family members and patients, the following exclusion criteria were used: 1) a history of stroke or transient ischemic attack (TIA); 2) neurological diseases (multiple sclerosis, AD, Parkinson’s disease); 3) a history of head trauma with more than 5-min loss of consciousness; 4) a current or past history of substance dependence; and 5) cardiovascular diseases (angina, hypertension, heart attack).

Table 1

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics of our sample.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCs (N = 55)</td>
</tr>
<tr>
<td>MCI patients (N = 68)</td>
</tr>
<tr>
<td>Group comparison</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>66.67 ± 10.65</td>
</tr>
<tr>
<td>68.62 ± 11.77</td>
</tr>
<tr>
<td>Gender (M/F)</td>
</tr>
<tr>
<td>33/22</td>
</tr>
<tr>
<td>38/30</td>
</tr>
<tr>
<td>MMSE</td>
</tr>
<tr>
<td>28.78 ± 1.10</td>
</tr>
<tr>
<td>26.62 ± 2.49</td>
</tr>
<tr>
<td>MoCA</td>
</tr>
<tr>
<td>26.33 ± 2.06</td>
</tr>
<tr>
<td>21.66 ± 3.06</td>
</tr>
<tr>
<td>CDR</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>t(121) = -0.95, p = 0.344</td>
</tr>
<tr>
<td>x^2 = 0.21, p = 0.646</td>
</tr>
<tr>
<td>(96.374) = 6.44, p = 0.001</td>
</tr>
<tr>
<td>(117.309) = 10.07, p &lt; 0.001</td>
</tr>
</tbody>
</table>

HCs, healthy controls; MCI, mild cognitive impairment. MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; CDR = Clinical Dementia Rating. For the three items of age, MMSE and MoCA, numbers represent mean ± standard deviation.

2.2. MRI acquisition

High-resolution T1-weighted three-dimensional images were acquired on a 3 Tesla MR scanner with an 8-channel head coil (Achieva 3.0 T TX dual Medical Systems; Philips Medical Systems, Eindhoven, Netherlands). Data acquisition details are summarized as follows: T1-weighted (three-dimensional fast field echo, TR = 9.7 ms, TE = 4.6 ms, flip angle = 8°); voxel dimensions = 1 × 1 × 1 mm^3; gap = 0; field of view = 256 × 256 × 192 mm^3; matrix = 256 × 256. High-resolution T1-weighted images were inspected by two experienced neuroradiologists, and no scanning artifacts or gross brain abnormalities were observed in any participant.

2.3. OFC sulcogyral pattern classification

Classifying sulcogyral patterns in the OFC was performed as reported in our previous studies (Li et al., 2015; Li et al., 2019).
Specifically, the OFC sulcogyral patterns were identified separately in each hemisphere using the medical image analysis software MRIcro (www.mccauslandcenter.sc.edu/mricro/) and classified according to the criteria proposed by Chiavaras and Petrides (2000). Regarding the sulci in the OFC, four main sulci have been identified, namely, the olfactory, medial (MOS), lateral (LOS), and transverse (TOS) orbital sulci. On the basis of the continuity of the MOS and LOS, the original work by Chiavaras and Petrides (2000) described three major types (Type I, II, and III) in each hemisphere (Fig. 1). In Type I pattern, rostral and caudal portions of the LOS (LOSr and LOSc) are continuous, whereas the rostral and caudal portions of the MOS (MOSr and MOSc) are clearly not connected (Fig. 1A). Compared with the Type I pattern, the distinctive feature of the Type II is that the rostral and caudal portions of both LOS and MOS are continuous, and both sulci are joined by TOS (Fig. 1B). In Type III pattern, the distinctive characteristic is that the rostral and caudal parts of both MOS and LOS are clearly not connected (Fig. 1C). The sulcus continuity was determined by evaluating several adjacent axial slices rather than focusing on one slice.

Two raters (Z.W. and Y.L.), who were blind to the sample, independently classified the OFC sulcogyral patterns across all participants. Accordingly, inter-rater reliability (Cohen's kappa) was 0.88 for the left hemisphere and 0.80 for the right hemisphere, respectively. All unclear classifications identified in the sample (i.e. 9% of the total sample) were reviewed by Y.L. and consensus was reached.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>MCI patients (N = 68)</th>
<th>HCs (N = 55)</th>
<th>HCs from Chiavaras and Petrides*</th>
<th>x²</th>
<th>p-value</th>
<th>BF₁₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>21 (31)</td>
<td>26 (47)</td>
<td>24 (48)</td>
<td>3.61</td>
<td>0.164</td>
<td>1.10</td>
</tr>
<tr>
<td>Type II</td>
<td>39 (57)</td>
<td>23 (41)</td>
<td>17 (34)</td>
<td>2.94</td>
<td>0.087</td>
<td>2.33</td>
</tr>
<tr>
<td>Type III</td>
<td>8 (12)</td>
<td>6 (12)</td>
<td>9 (18)</td>
<td>0.02</td>
<td>0.882</td>
<td>0.28</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>28 (41)</td>
<td>32 (58)</td>
<td>32 (64)</td>
<td>7.49</td>
<td>0.024</td>
<td>6.95</td>
</tr>
<tr>
<td>Type II</td>
<td>36 (53)</td>
<td>16 (29)</td>
<td>13 (26)</td>
<td>7.09</td>
<td>0.008</td>
<td>14.68</td>
</tr>
<tr>
<td>Type III</td>
<td>4 (6)</td>
<td>7 (13)</td>
<td>5 (10)</td>
<td>1.01</td>
<td>0.315</td>
<td>0.58</td>
</tr>
<tr>
<td>Total (L + R)</td>
<td>95.20</td>
<td>99.09</td>
<td>10.98</td>
<td>9.52</td>
<td>0.009</td>
<td>9.58</td>
</tr>
</tbody>
</table>

MCI, mild cognitive impairment; HCs, healthy controls. Note: *Analyses comparing the distribution of OFC sulcogyral patterns between groups in the present study. †Data from the HCs (n = 50) of Chiavaras and Petrides (2000) is included in the table for ease of comparison. Because pairwise group comparison analysis involved three statistical tests (one per OFC subtype), we used a Bonferroni-corrected significance threshold of 0.05/3 = 0.017.
some of the subsequent analyses.

Across both hemispheres, our \(x^2\) analysis demonstrated that the OFC sulcogyral pattern distribution in MCI patients was significantly different from that observed in HCs \((x^2 = 9.52, \text{Cramer’s } \gamma = 0.197, p = 0.009)\). To further quantify the evidence supporting the between-group difference, we conducted a Bayesian contingency table analysis based on a Poisson sampling model (Jamil et al., 2017). The resulting Bayes Factor \((BF_{10} = 10.98)\) demonstrated that our data was about 11 times more likely to be related to the hypothesis of a between-group difference than under the null hypothesis. The reported Bayes Factor is considered strong evidence supporting the alternative hypothesis of a relationship between the group and OFC sulcogyral pattern distribution across both hemispheres (Jamil et al., 2017). Post-hoc tests further revealed that the difference between groups was mainly driven by significant increased prevalence of Type II pattern \((55\% \text{ vs } 35\%, x^2 = 9.48, \text{Cramer’s } \gamma = 0.196, p = 0.002)\) and decreased prevalence of Type I pattern \((36\% \text{ vs } 53\%, x^2 = 6.90, \text{Cramer’s } \gamma = 0.167, p = 0.009)\) in MCI patients compared with HCs (Table 2, Fig. 2). The corresponding Bayes Factor confirmed this result, showing very strong evidence for a different proportion of Type II pattern \((BF_{10} = 35.71)\) and strong evidence for a different proportion of Type I pattern \((BF_{10} = 9.58)\) between groups. When investigating each hemisphere respectively, the difference between groups is still significant in the right hemisphere \((x^2 = 7.49, \text{Cramer’s } \gamma = 0.247, p = 0.024)\) (Table 2, Fig. 2). The associated Bayes Factor \((BF_{10} = 6.95)\) supported this result, showing moderate evidence in line with the hypothesis of a relationship between the group and OFC sulcogyral pattern distribution in the right hemisphere. Post-hoc tests further revealed that the between-group difference was primarily contributed by a significantly enhanced frequency of Type II pattern \((53\% \text{ vs } 29\%, x^2 = 7.09, \text{Cramer’s } \gamma = 0.240, p = 0.008)\) in MCI patients compared with HCs. The associated Bayes Factor \((BF_{10} = 14.68)\) confirmed this result, showing strong evidence for a different proportion of Type II pattern between groups. In contrast, we found no significant difference in the distribution of Type I pattern in the left \((x^2 = 3.61, p = 0.164, BF_{10} = 1.10)\) and right hemisphere \((x^2 = 3.52, p = 0.061, BF_{10} = 2.47)\). Note that though the distribution of OFC sulcogyral patterns was very similar between the left and right hemispheres in either HCs \((x^2 = 1.95, p = 0.376, BF_{10} = 0.54)\) and patients with MCI \((x^2 = 2.45, p = 0.293, BF_{10} = 0.50)\). In addition, we found no significant difference in the Type III pattern distribution between groups in each hemisphere (left: \(x^2 = 0.0, p = 0.882, BF_{10} = 0.28\); right: \(x^2 = 1.01, p = 0.315, BF_{10} = 0.58\) and across both hemispheres \((x^2 = 0.60, p = 0.440, BF_{10} = 0.26)\) (Table 2, Fig. 2).

In left/right hemisphere combinations, a total of 30.9% of MCI patients (compared with 14.5% of HCs) had a Type I \((x^2 = 4.50, \text{Cramer’s } \gamma = 0.191, p = 0.034)\) and 8.8% of MCI patients (compared with 27.3% of HCs) had a Type I \((x^2 = 7.31, \text{Cramer’s } \gamma = 0.244, p = 0.007)\). Furthermore, a total of 79.4% of MCI patients (compared with 56.4% of HCs) had at least one hemisphere with a Type II pattern \((x^2 = 7.57, \text{Cramer’s } \gamma = 0.248, p = 0.006)\), and 63.2% of MCI patients (compared with 78.2% of HCs) had at least one hemisphere with a Type I pattern \((x^2 = 3.23, p = 0.072)\). In terms of relative risk, participants with a Type II pattern in both hemispheres showed a 1.45-fold risk for being MCI, compared with those who had only one or zero Type II pattern in either hemisphere. Participants with a Type I pattern in both hemispheres showed a 0.47-fold risk for being MCI, compared with those who had only one or zero Type I pattern in either hemisphere. Furthermore, participants with at least one hemisphere with a Type II pattern showed a 1.72-fold risk for being in the MCI group, compared with those without any Type II pattern. Last, participants with at least one hemisphere with a Type I pattern showed a 0.74-fold risk for being MCI, compared with those without any Type I pattern.

### 3.2. OFC sulcogyral patterns and cognitive measures

We employed categorical regression analyses to examine the potential relationship between sulcogyral pattern types in the OFC and cognitive functions measured by MMSE and MoCA, as described in previous studies (Li et al., 2019; Nakamura et al., 2018). For MCI patients, no significant relationship existed between OFC sulcogyral pattern types and cognitive measures (MMSE: overall fit: \(F(3,57) = 0.28, p = 0.841 - \text{standardized coefficients}: \beta_{\text{Type I}} = 0.12, F = 1.18, p = 0.282; \beta_{\text{Type II}} = 0.12, F = 0.89, p = 0.350; \beta_{\text{Type III}} = 0.10, F = 0.58, p = 0.448; \text{MoCA: overall fit: } F(3,57) = 1.24, p = 0.302 - \text{standardized coefficients}: \beta_{\text{Type I}} = 0.15, F = 1.99, p = 0.164; \beta_{\text{Type II}} = 0.14, F = 1.10, p = 0.298; \beta_{\text{Type III}} = 0.16, F = 1.65, p = 0.204). Similarly, for healthy controls, no significant relationship was found between OFC sulcogyral pattern types and cognitive measures (MMSE: overall fit: \(F(3,48) = 0.47, p = 0.708 - \text{standardized coefficients}: \beta_{\text{Type I}} = 0.10, F = 0.41, p = 0.526; \beta_{\text{Type II}} = 0.02, F = 0.02, p = 0.883; \beta_{\text{Type III}} = 0.12, F = 0.57, p = 0.453; \text{MoCA: overall fit: } F(3,48) = 2.33, p = 0.086 - \text{standardized coefficients}: \beta_{\text{Type I}} = 0.11, F = 0.40, p = 0.528; \beta_{\text{Type II}} = 0.12, F = 0.70, p = 0.406), except for the relationship between Type I pattern and MoCA (standardized coefficients: \(\hat{\beta}_{\text{Type I}} = 0.40, F = 8.20, p = 0.006\)). Finally, for all participants, no significant relationship existed between OFC sulcogyral pattern types and cognitive measures (MMSE: overall fit: \(F(3,109) = 0.82, p = 0.486 - \text{standardized coefficients}: \beta_{\text{Type I}} = 0.02, F = 0.05, p = 0.818; \beta_{\text{Type II}} = 0.17, F = 2.24, p = 0.137; \beta_{\text{Type III}} = 0.11, F = 0.91, p = 0.343; \text{MoCA: overall fit: } F(3,109) = 0.57, p = 0.633 - \text{standardized coefficients}: \beta_{\text{Type I}} = 0.05, F = 0.28, p = 0.598; \beta_{\text{Type II}} = 0.07, F = 0.28, p = 0.598; \beta_{\text{Type III}} = 0.05, F = 0.19, p = 0.660\)).
OFC sulcogyral patterns in MCI patients. Specifically, we found that MCI patients exhibited an increased proportion of Type II pattern compared with HCs, particularly within the right hemisphere. Meanwhile, MCI patients also exhibited decreased proportion of Type I pattern compared with HCs in both hemispheres. Regarding OFC sulcogyral patterns, Type I pattern is the most common type in HCs and has been argued to be a standard folding that is essential for efficient communication between and within brain regions (Patti and Troiani, 2018). Therefore, Type I pattern is thought to be associated with a potential protective mechanism that may reduce the likelihood of neuropsychiatric conditions (Bartholomeusz et al., 2013; Patti and Troiani, 2018). Moreover, consistent with previous findings that increased proportions of the less common patterns are associated with neuropsychiatric disorders (Bartholomeusz et al., 2013; Chakirova et al., 2010; Lavoie et al., 2014; Takayanagi et al., 2010), we also found an association of an increased proportion of Type II pattern with MCI. Such deviations from the standard OFC sulcogyr patterns likely lead to suboptimal signaling that manifest as atypical cognitive traits in MCI patients. Note, an increased proportion of Type II pattern was lateralized to the right hemisphere in MCI patients, which supports the notion that the potential protective mechanism is more robust in the right hemisphere, as argued in previous studies (Bartholomeusz et al., 2013; Nakamura et al., 2007; Patti and Troiani, 2018). Taken together, our results suggest that an altered distribution of Type I and Type II patterns may represent a premorbidity structural marker of MCI.

The altered distribution of OFC sulcogyral patterns may have potential implications for understanding early pathological conditions of MCI, especially when considering the lack of early, more sensitive and reliable biological markers to anticipate diagnostic options. For the pathology in these patients. In the research literature on MCI patients, the majority of studies on MCI emphasize functional and structural abnormalities over the entorhinal and hippocampal regions (Balota and Duchek, 2015; Dickerson et al., 2005; Douaud et al., 2013; Sperling, 2007). In contrast, a clear picture is still lacking on how the frontal lobe, especially the OFC, is affected in MCI patients although some brain imaging studies have reported functional and structural abnormalities in the OFC in these patients (Driscoll et al., 2009; Hämäläinen et al., 2007; Han et al., 2011; Schroeter et al., 2009; Seo et al., 2010; Singh et al., 2006). Our findings strengthen the existing evidence in support of a pathological role of the OFC in MCI (Clark et al., 2018). Given the organization of sulcogyral patterns initiates in the prenatal period and are stable throughout the human life span (Armstrong et al., 1995; White et al., 2010), our results also could be related to a neurodevelopmental origin of age-related cognitive decline in MCI. This argument is in line with the results of previous studies on neuropsychiatric disorders, such as substance abuse. Previous studies have showed that pre-existing structural traits in the OFC can predict the amount of later substance use in adolescents (Cheetham et al., 2012; LotfiPour et al., 2009). Similarly, Chye et al. (2017) have found that cannabis users with an altered distribution of OFC sulcogyral patterns consumed more cannabis over their lifetime. Based on such findings, our preliminary results seem to support an idea that neurodevelopmental structural traits in the OFC might predispose to MCI in aging, although this requires further confirmation in future studies.

From a mechanistic perspective, a key question is how OFC sulcogyral patterns variability may influence individuals’ vulnerability to develop MCI and lead to subsequent dementia such as Alzheimer’s disease (AD). A possible answer may be to determine the individual variability along OFC connectivity. It has been demonstrated that cortical folding patterns are constrained by white matter connections and are thus argued to sustain structural (Van Essen, 1997; Zilles et al., 2013) and functional connectivity (Mueller et al., 2013). Thus, the altered distribution of OFC sulcogyr patterns in MCI patients may indicate altered connectivity patterns that may in turn modulate important cognitive functions associated to the OFC. Altered distribution of OFC sulcogyr patterns and associated changes in OFC connectivity might also be associated with cognitive impairment observed in MCI patients. In particular, Type I pattern has been related with improved cognitive functions including IQ, perceptual processing and positive emotions in healthy controls (Nakamura et al., 2007). Meanwhile, individuals with prevalence of OFC sulcogyr Type I pattern and increased prevalence of OFC sulcogyr Type II pattern have been associated with increased physical anhedonia (Zhang et al., 2016). Thus, these findings indicate that OFC sulcogyr pattern Type II pattern may serve as a neurodevelopmental risk marker, while OFC sulcogyr pattern Type I pattern may be somewhat protective. Interestingly, in healthy individuals, OFC sulcogyr pattern Type III pattern has also been associated with improved executive control (Nakamura et al., 2007), a key cognitive domain to define MCI features. In the present study, a trend towards lower prevalence of Type III pattern in MCI patients compared with healthy controls was found, consistent with previous evidence reporting regulatory control deficits in MCI patients (Traykov et al., 2007).

Our study counts with several strengths and weaknesses. The use of Frequentist and Bayesian statistics, and applied stringent Bonferroni correction for multiple comparisons where appropriate is a solid strength of our methodology. However, this study counts with several limitations. First, the interpretation of our structural brain results in terms of functional consequences is limited by the absence of functional assessments, such as brain activity measures. Future work needs to elucidate the link between OFC sulcogyral patterns and their functional implications. Second, we did not find a relationship between OFC sulcogyral patterns and general cognitive functions as indexed by MMSE and MoCA scores. While this might sound surprising, several studies as well fail to report such an association in schizophrenia and behavioral addiction without significant relationships (Bartholomeusz et al., 2013; Takayanagi et al., 2010). As discussed by these studies, the OFC sulcogyr patterns may not affect disease progression or possibly later in the course of the disease. Third, MCI presents an heterogeneous clinical manifestation and thus each specific subtype may have specific underlying pathology (Petersen et al., 2014). In fact, our findings may be suitable pre-morbid markers of pathological conditions for specific subtypes of MCI. Yet, future work is required including a larger sample with distinct MCI subgroups to shed some light on this potential application of our results. Fourth, among the criteria for MCI, the most widely used are those proposed by Petersen et al. (1999; 2001) (Petersen et al., 2001; Petersen et al., 1999), which are the diagnosis criteria for MCI adopted in the present study. Compared with an alternative method of diagnosing MCI proposed by Jak and Bondi (the Jak/Bondi criteria) (Bondi et al., 2008; Jak et al., 2009), this conventional method may produce more ‘false positive’ diagnostic errors (Bondi et al., 2014). To further address this issue, future work may apply alternative neuropsychological criteria for MCI diagnosis from Jak and Bondi. This approach may lead to more reliable results because of removal of ‘false positive’ cases. Last but not least, MoCA and MMSE are the sole cognitive measures to classify individuals as cognitively normal or impaired cognition in the present study. Comprehensive neuropsychological evaluation was not performed on our sample, rendering the evaluation of other cognitive domains not possible. Therefore, the use of a full range of neuropsychological test measures would help improve diagnostic rigor for MCI in future work. Despite these limitations, we think that our findings are still robust and may foster further research on neuroanatomical characteristics and pathological signatures in MCI patients.

In conclusion, the present study aimed at characterizing the distribution of OFC sulcogyr patterns in patients with MCI. Patients with MCI exhibited an increased proportion of Type II pattern compared with HCs, especially in the right hemisphere. MCI patients also showed a decreased proportion of Type I pattern compared with healthy controls in both hemispheres. To the best of our knowledge, our results
provide novel evidence for a skewed distribution of OFC sulcogyral patterns in patients with MCI, thereby suggesting that an altered distribution of Type I and Type II patterns might represent a premorbid structural marker of MCI. Since this was an exploratory and preliminary study, it turns fundamental to replicate our results in an independent and larger sample. Also, given the many similarities between MCI and MCI converting to dementia such as AD, future work should examine whether the increased prevalence of Type II pattern and decreased prevalence of Type I could also be found in dementia such as AD, and thus test whether the altered distribution of OFC sulcogyral patterns reflects a more general trait in this disease. Ultimately, it will be crucial to design studies jointly assessing structural and functional alterations, in order to better understand their relationship.

Author contributions

Y.L. conceived and designed the study; B.Z., X.Y., Z.Q., and J.L. collected the data; Y.L. and Z.W. analyzed the data; Y.L. wrote and edited the draft manuscript; B.Z. commented on the manuscript. I.O. provided diligent proofreading of this manuscript.

Declaration of Competing Interest

None

Acknowledgments

Yansong Li was supported by the National Natural Science Foundation of China (Grant No. 31600929) and the Fundamental Research Funds for the Central Universities (I01901480002). Bing Zhang was supported by the National Natural Science Foundation of China (81720108022), the Fundamental Research Funds for the Central Universities at Nanjing University (2020-021414304062), The key project of Jiangsu Commission of Health (K2019025), The social development project of science and technology project in Jiangsu Province (BE20177007), The key medical talents of the Jiangsu province, the “13th Five-Year” health promotion project of the Jiangsu province (ZDRC2016064), Jiangsu Provincial Key Medical Discipline (Laboratory) (ZDXKA2016020) and the project of the sixth peak of talented people (WSN -138). Xin Zhang was supported by National Natural Science Foundation of China (81971596). Zhao Qing was supported by National Natural Science Foundation of China (81701672). I.O. was supported by Miguel Servet ISCIII-CP18/00038.

References

schizophrenia. Brain 130, 693–707.


