MOOD AND COGNITION IN OLD AGE

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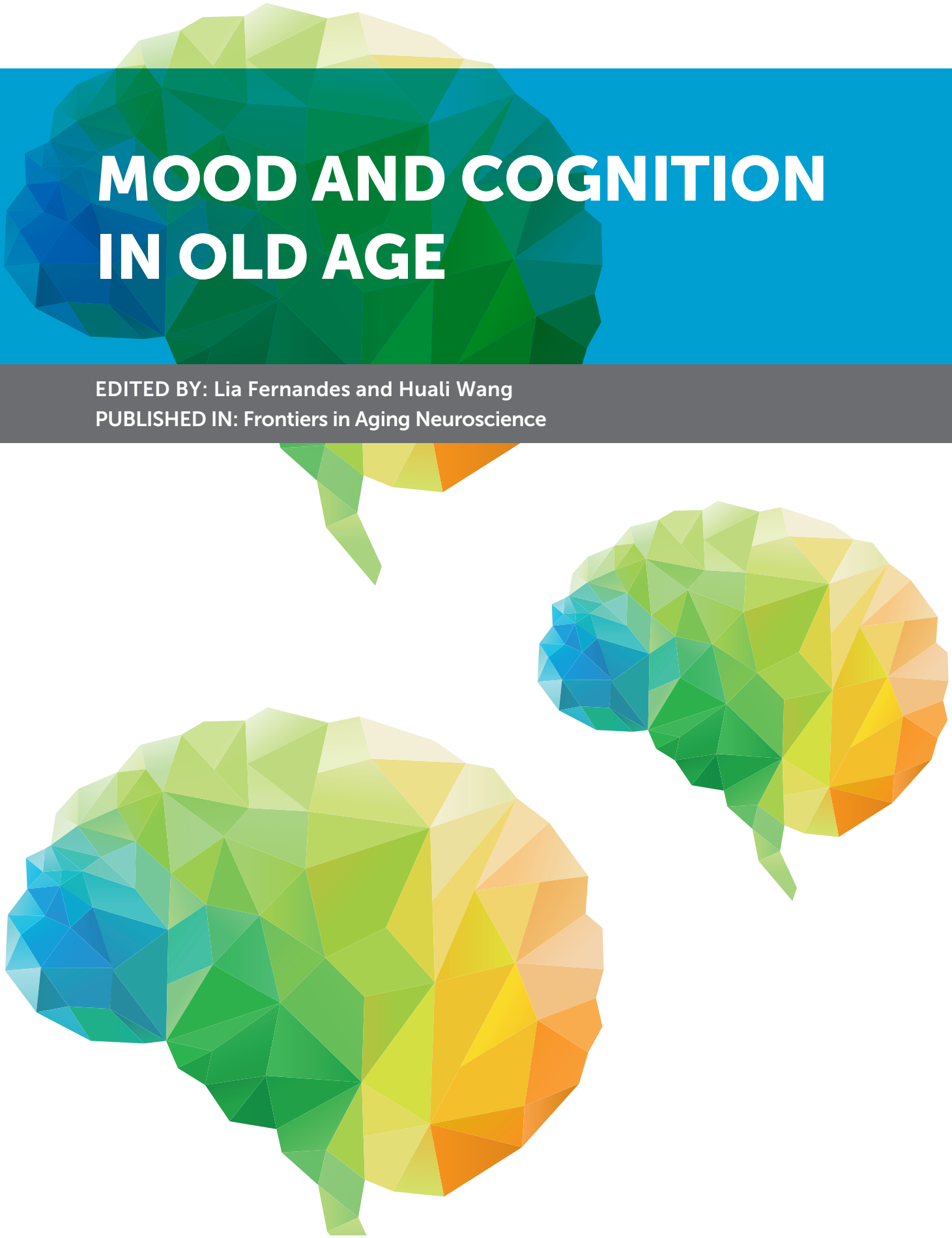

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MOOD AND COGNITION IN OLD AGE

Topic Editors:
Lia Fernandes, Universidade do Porto, Portugal
Huali Wang, Peking University Sixth Hospital, China

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EDITORIAL
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Editorial: Mood and Cognition in Old Age

Lia Fernandes[1,2] *and Huali Wang*[3]*

[1] Department of Clinical Neuroscience and Mental Health, Faculty of Medicine, University of Porto, Porto, Portugal, [2] Research Unit CINTESIS—University of Porto, Porto, Portugal, [3] Beijing Dementia Key Lab, National Clinical Research Center for Mental Disorders, Peking University Institute of Mental Health (Sixth Hospital), Beijing, China

Keywords: mood disorder, mild cognitive impairment, Alzheimer's disease, neuroimaging, psychology

Editorial on the Research Topic

Mood and Cognition in Old Age

Depression and cognitive impairment are great challenges for the elderly population. The Research Topic "Mood and Cognition" by Frontiers in Aging Neurosciences comprises 16 articles addressing new findings and perspectives concerning mood and cognition in old age, including age-related disorders (e.g., elderly depression, mild cognitive impairment, and Alzheimer's disease). The articles presented focus on the role of the brain structure and activity in mood and cognition and explore several hypotheses regarding their association with new pathophysiological processes such as inflammation, the association with other comorbidities, as well as the impact of invasive medical procedures on cognition and delirium. Other approaches are focused on the influence of socialization, interpersonal relations, and social learning on cognitive performance and quality of life.

Three articles are focused on the connection between dementia (Alzheimer's Disease-AD) and depression. Liu et al., conducted a study explaining how the hypothalamus interacts with other brain regions in AD patients with depression (D-AD), using a functional connectivity (FC) analysis. This promising study showed that D-AD patients had reduced FC in the hypothalamus, the right middle temporal gyrus and the right superior temporal gyrus compared with the FC of nD-AD patients, and suggested that the abnormal FC between the hypothalamus and the temporal lobe may play a key role in the pathophysiology of depression in AD patients. Lebedeva et al., assessed whether structural brain magnetic resonance imaging (MRI) in late-life depressed patients (LLD) could predict mild cognitive impairment or dementia 1 year prior to the diagnosis. The authors concluded that the analysis of the baseline structural MRI alone was able to accurately distinguish LLD patients developing MCI and dementia, from those remaining cognitively stable. Moreover, the authors showed that the ventral diencephalon, including the hypothalamus, might play an important role in the preservation of cognitive functions in LLD. Following the same line, Liu et al. investigated the relationship among a history of depression, depressive states, and dementia in a community-based old-old cohort in Japan. This valuable study concluded that a history of depression should be considered a risk factor for all-cause dementia and that, in the old-old population, depression was associated with a higher prevalence of dementia, lower cognitive performance, and a smaller hippocampus. The study of Hou et al. examined the implicit relationship between the disruption of interhemispheric functional coordination and cognitive impairment in late-onset depression (LOD), using functional magnetic resonance imaging (fMRI). The authors state that the altered linkage patterns of intrinsic homotopic connectivity and impaired cognitive flexibility may constitute a novel clue regarding the neural substrates underlying cognitive impairment in LOD.

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Thomas Wisniewski,
New York University, United States

***Correspondence:**
Huali Wang
huali_wang@bjmu.edu.cn

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Zhao et al. present a hypothesis and theory article focusing on post-stroke depression (PSD), which is a common neuropsychiatric complication in patients who have suffered a stroke. The authors explored the inflammation hypothesis for PSD and point to preventive and therapeutic strategies, specifically remote ischemic conditioning (RIC). They concluded that RIC may be a novel approach to prevent PSD, with potential to be widely used in clinical practice and to be applied in other neurobehavioral disorders.

Moretti and Signori conducted a very interesting review regarding the neural correlates for apathy in frontal-prefrontal and parietal cortical-subcortical circuits. In spite of the controversial definitions, with different categorizations of this nosographical entity, the present discussion may contribute to new insights about apathy in the context of several pathologies being degenerative, vascular, acute, or chronic. The authors concluded by highlighting important future directions toward goal-specific problems.

In their article Gamaldo et al. examine the rates, predictors, and outcomes of sleep disturbances in older hospitalized patients. This is the first study to use a large national (USA) healthcare database, with 35,258,031 of older adults. Stating that the proportion of older adults with a sleep diagnosis has increased significantly over the last decade, this study documented an important association between increasing sleep disturbance rates and expenditures within hospital settings. Moreover, co-morbidities such as depression, cardiovascular risk factors, and neurological disorders steadily increased over time in these patients. Also from the USA, Assari and Lankarani conducted a study focused on the reciprocal and longitudinal associations between depressive symptoms and mastery, comparing black and white American older adults. They found that, among white but not black older adults, higher levels of depressive symptoms at baseline predicted a greater decline in sense of mastery over 3 years' follow-up, stating that race may alter how depression is linked to changes in evaluation of self (e.g., mastery) over time.

Focusing on cognition, the article of Palaci et al. explored how parental economic socialization affects the planning for retirement (FPR) through the mediation of financial literacy, financial planning decisions, and financial management. The results show that parental economic socialization directly and indirectly influences FPR, and that parental economic behavior acts as a positive model for the development of financial literacy and skills and for decisions about FPR. Based on this, the authors point out important future lines of research.

Ouanes et al. conducted a population-based study, hypothesizing that increased cortisol may be associated with poorer cognition and with certain personality traits (mainly high neuroticism), and that personality might explain the association between cortisol and cognition. This study found that high agreeableness and openness might be associated with poorer executive performance in later life. Moreover, increased cortisol may be associated with both specific personality traits (high extraversion, low openness) and worse cognitive performance. In spite of this, the authors concluded that the association between personality traits and cognitive impairment seems to be independent of increased cortisol production and its effects on cognition.

Two articles are specifically dedicated to Alzheimer Disease (AD). The article from Wang et al. explored the interaction dynamics between different electroencephalographic (EEG) oscillations in AD patients, comparing the resting eye-closed EEG signals in AD patients and healthy volunteers. The authors propose that the pathological increase of ongoing gamma-band power might result from the disruption of the GABAergic interneuron network in AD patients. They also suggest that the cross-frequency overcouplings, might indicate the attenuated complexity of the neuronal network, and that AD patients have to use more neural resources to maintain the resting brain state. These promising findings provide new evidence of the disturbance of the brain oscillation network in AD and further deepen the understanding of the central mechanisms of AD. Focused on the genetics of the disease, Lukiw et al. provide recent evidence for the mis-regulation of a small family of genes expressed in the human hippocampus that appear to be significantly involved in the expression patterns common to both AD and aggression. The magnitude of genes expression implicated in aggressive behavior appears to be more pronounced in the later stages of AD when compared to MCI. These recent genetic data further indicate that the extent of cognitive impairment may have some bearing on the degree of aggression which accompanies the AD phenotype.

Two other important articles focused on delirium. El-Gabalawy et al. developed a novel stress-diathesis model based on comprehensive pre-operative psychiatric and neuropsychological testing, a blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) carbon dioxide (CO_2) stress test, and high fidelity measures of intra-operative parameters that may interact facilitating post-operative delirium (POD). Results provide preliminary support for the interacting of diatheses (vulnerabilities) and intra-operative stressors on the POD phenotype. Based on these initial findings, the authors offer some recommendations for intra-operative management for patients at risk of POD. The article from Dong et al. presents the results of a clinical investigation on the associations between the preoperative expression levels of microRNA (miR)-146a, miR-125b, and miR-181c in cerebrospinal fluid (CSF) and serum and the development and severity of post-operative delirium (POD). It found that dysregulation of preoperative miR-146a and miR-181c in CSF and serum was associated with the development and severity of POD, and that these NeurimmiRs might participate in the neuropathogenesis of POD.

Also exploring cognitive changes after invasive medical procedures, Kulason et al. present preliminary results of a pilot study, being the first report to examine Postoperative Cognitive Decline (POCD) after major thoracic surgery (partial pulmonary lobectomy lung) in elderly Japanese patients. This pioneer study clarified that decline in cognition is detectable to a certain extent after the surgery. Additionally, longer anesthetic exposure may negatively impact on attention and working memory, and preoperative mental well-being is a possible predictor of POCD.

Cleutjens et al. investigated whether macrostructural brain MRI features of cerebral small vessel disease (SVD) and hippocampal volume (HCV) are related to cognitive performance in patients with chronic obstructive pulmonary disease (COPD). No group differences were reported, regarding demographics, clinical characteristics, comorbidities and the presence of SVD features and HCV. This way, the authors concluded that there is not yet evidence for a relationship between cerebral SVD and HCV and cognitive functioning in patients with COPD and that additional studies will be needed to determine other possible mechanisms of cognitive impairment in these patients.

In all, this Research Topic may contribute to building different perspectives on how mood and cognition in late life could be influenced by the brain structure, activity and aging, and how this may interact with environmental stimuli and interpersonal relationships. All these studies would enrich our understanding of the bio-psycho-social mechanisms underlying improving psychological well-being and cognitive health.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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The Abnormal Functional Connectivity between the Hypothalamus and the Temporal Gyrus Underlying Depression in Alzheimer's Disease Patients

Xiaozheng Liu[1], Wei Chen[1], Yunhai Tu[2], Hongtao Hou[3], Xiaoyan Huang[1], Xingli Chen[3], Zhongwei Guo[3], Guanghui Bai[1]* and Wei Chen[4,5]**

[1]China-USA Neuroimaging Research Institute, Department of Radiology of the Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou, China, [2]Eye Hospital, Wenzhou Medical University, Wenzhou, China, [3]Tongde Hospital of Zhejiang Province, Hangzhou, China, [4]Department of Psychiatry, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine and the Collaborative Innovation Center for Brain Science, Hangzhou, China, [5]Key Laboratory of Medical Neurobiology of Chinese Ministry of Health, Hangzhou, China

Hypothalamic communication with the rest of the brain is critical for accomplishing a wide variety of physiological and psychological functions, including the maintenance of neuroendocrine circadian rhythms and the management of affective processes. Evidence has shown that major depressive disorder (MDD) patients exhibit increased functioning of the hypothalamic-pituitary-adrenal (HPA) axis. Neurofibrillary tangles are also found in the hypothalamus of Alzheimer's disease (AD) patients, and AD patients exhibit abnormal changes in the HPA. However, little is known of how the hypothalamus interacts with other brain regions in AD patients with depression (D-AD). Functional connectivity (FC) analysis explores the connectivity between brain regions that share functional properties. Here, we used resting-state (rs) magnetic resonance imaging (MRI) technology and the FC method to measure hypothalamic connectivity across the whole brain in 22 D-AD patients and 21 non-depressed AD patients (nD-AD). Our results showed that D-AD patients had reduced FC among the hypothalamus, the right middle temporal gyrus (MTG) and the right superior temporal gyrus (STG) compared with the FC of nD-AD patients, suggesting that the abnormal FC between the hypothalamus and the temporal lobe may play a key role in the pathophysiology of depression in AD patients.

Keywords: Alzheimer's disease, depression, functional magnetic resonance imaging, functional connectivity, hypothalamus

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Edited by:
Lia Fernandes, Universidade do Porto, Portugal

Reviewed by:
Yonggui Yuan, Southeast University, China
Pierrette Gaudreau, Université de Montréal, Canada

Correspondence:
Zhongwei Guo
guozw1977@aliyun.com
Guanghui Bai
bghu79@126.com
Wei Chen
srrcw@zju.edu.cn

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INTRODUCTION

Symptoms of major depression of varying severity are a common comorbidity in Alzheimer's disease (AD), with a prevalence of up to 63% in patients with AD (Khundakar and Thomas, 2015). In addition, these symptoms result in more rapid functional decline and loss of independence, and even shorter survival lengths (Lyketsos and Lee, 2004; Chi et al., 2015). Although both psychiatric and neurological disorders recognize the occurrence of affective and psychotic symptoms in patients with AD, the underlying mechanisms of depressive symptoms in these patients

still remain unclear. Certain AD studies have emphasized psychosocial factors, such as functional and cognitive disabilities, whereas others have stressed neurobiological underpinnings. Improved knowledge of the neurobiological basis is required for the development of more effective treatment strategies (Khundakar and Thomas, 2015).

The current research considers the hypothalamo-pituitary-adrenal (HPA) axis, which mediates stress responses, one major pathway for depressive symptomatology (Schindler et al., 2012). HPA axis activity is governed by the secretion of adrenocorticotropic hormone-releasing factor (CRF) and vasopressin (AVP) from the hypothalamus, which, in turn, activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary, which ultimately stimulates the secretion of glucocorticoids from the adrenal cortex (Nemeroff, 1996). The neuropeptides, CRF and AVP, are released within the paraventricular nucleus (PVN) of the hypothalamus and are crucially involved in the pathogenesis of depression (Bao et al., 2008). Studies over the last 40 years have shown HPA axis hyperactivity as one of the most consistent biological findings in major depressive disorder (MDD). Meanwhile, with the development of medical imaging, numerous neuroimaging studies have investigated the neurobiological roles of the hypothalamus in MDD patients (Baeken et al., 2009; Gao et al., 2013; Sudheimer et al., 2015).

Baeken et al. (2009) examined the emotional and neurobiological effects of one session of high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) applied to the left dorsolateral prefrontal cortex on a sample of unipolar treatment-resistant depressed patients of the melancholic subtype. To examine possible time delays in the HF-rTMS effects, mood and salivary cortisol were assessed not only immediately after the sessions but also after a period of 30 min. They found support for the hypothesis that a single session has a significant impact on the HPA axis, as measured by salivary cortisol. Additionally, Gao et al. (2013) found diminished GABAergic input to the hypothalamus upon postmortem examinations of MDD patients. Using resting-state functional magnetic resonance imaging (rsfMRI) and functional connectivity (FC) analyses, Sudheimer et al. (2015) reported that MDD patients show reduced FC between the hypothalamus and the subgenual cortex compared with the FC of healthy participants. Further, increased cortisol secretion and reduced connectivity were both found to be associated with MDD severity.

It is well known that hypothalamic communication with the rest of the brain is crucial for a wide variety of physiological and psychological functions, e.g., managing affective processes and maintaining neuroendocrine circadian rhythms. To accomplish these functions, the hypothalamus maintains neural connections within the brain and coordinates a variety of neuroendocrine cascades that influence target tissues throughout the body. However, little is known of how the hypothalamus interacts with other brain regions in mild AD patients with depression (D-AD). FC is defined as temporal correlations between spatially remote neurophysiological events or functional interactions (Büchel and Friston, 2000). Given that the hypothalamus may be significantly involved in MDD, we hypothesized that fMRI FC between the hypothalamus and emotional processing areas of the brain would be abnormal in D-AD patients compared with that of non-depressed AD (nD-AD) patients.

Thus, here we used the hypothalamus as a "seed" to investigate FC changes in D-AD patients and assessed the correlation between the FC changes and depressive symptom severity.

MATERIALS AND METHODS

Patients

The sample group was composed of 21 nD-AD patients and 22 D-AD patients, recruited from Tongde Hospital in Zhejiang Province, China. Diagnoses were confirmed using the National Institute on Aging-Alzheimer's Association guidelines (McKhann et al., 2011), with scores of 20–24 on the Mini-Mental State Examination (MMSE) and 1 on the Clinical Dementia Rating scale (CDR). Patients were screened to exclude those with histories of alcoholism, smoking, neurological disorders, or psychiatric disorders and those who were taking antidepressant medication. Patients were also excluded if the dual-echo MRI images showed two or more hyperintense lesions with diameters $\geq$5 mm or more than four hyperintense lesions with diameters 0–5 mm. All patients were right-handed, had more than 6 years of education and were 65–80 years old. This study was carried out in accordance with the recommendations of the Declaration of Helsinki and the principles of good clinical practice, the Ethics Committee of Tongde Hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the the Ethics Committee of Tongde Hospital.

The diagnoses of depression were determined by two trained psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; Gmitrowicz and Kucharska, 1994). In brief, all D-AD patients exhibited one or more of two core criteria (depressed mood, loss of interest, or pleasure) lasting for >2 weeks. Depression severity was evaluated using the Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1967) and the Neuropsychiatric Inventory (NPI; Cummings et al., 1994). The scores on the HAMD-17 range between 7 and 17, and for the depression domain of the NPI (D-NPI), scores $\geq$4 are typically considered indicative of clinical significance (Schneider et al., 2001).

MRI Scanning

MRI scanning was performed at mid day and patients were fasted for at least 6 h before MRI examination. Imaging data were acquired using a 3T Siemens scanner (Siemens Magnetom Verio; Siemens Medical Systems, Erlangen, Germany) at Tongde Hospital. All patients were placed in a birdcage head coil, with foam padding fitted to reduce head motion. rs fMRI scans were obtained using a gradient echo T2*-weighted sequence with the following parameters: 33 axial slices, thickness/gap = 4.8/0 mm, in-plane resolution = 64 × 64, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms,

flip angle = 90° and field of view (FOV) = 200 × 200 mm^2. Each condition consisted of 200 functional volumes. During the functional runs, patients were instructed to remain awake with their eyes closed. Additionally, high-resolution T1-weighted whole brain magnetization prepared rapid gradient echo images were obtained using the following parameters: 128 sagittal slices, slice thickness/gap = 1/0 mm, in-plane resolution = 512 × 512, TR = 1900 ms, TE = 2.48 ms, inversion time (TI) = 900 ms, flip angle = 9° and FOV = 256 × 256 mm^2.

T1-weighted Images

To investigate the effects of gray matter (GM) volume on the FC analyses, we performed voxel-based morphometry on the T1-weighted images using the VBM8 toolbox in SPM8[1]. T1-weighted images were spatially normalized to the T1-weighted space (Montreal Neurological Institute, MNI[2]). Following this normalization, the resulting images were automatically segmented into GM, white matter (WM) and cerebrospinal fluid (CSF). Finally, the segmented images were nonlinearly modulated to compensate for spatial normalization effects, and individual GM volumes (GMVs) of the whole brain were calculated. The GMVs were compared between the two groups using two-sample two-tailed *t*-tests.

rsfMRI Data Processing

All rsfMRI data preprocessing was performed using SPM8[1] and the Data Processing Assistant for Resting State fMRI[3] software. The preprocessing consisted of removing the first 10 volumes of the functional images, slice timing correction and motion correction. In regard to the motion correction, all participants had <1.5 mm maximum displacement in the x-, y-, or z-axes, with 1.5° of angular motion during the entire rsfMRI scan. Then, we compared the mean absolute displacement of head motion, and there was no significant difference between the two groups in regard to mean motion. The functional images were then coregistered to a high-resolution anatomical scan, normalized to the MNI space, and resampled at 3 mm^3. The normalized images were smoothed using a Gaussian kernel of 6 mm^3 full-width half-maximum (FWHM). Finally, temporal filtering was used to extract the signals in the 0.01–0.08-Hz frequency band, followed by linear regression to factor out six head motion parameters, along with the average CSF and WM signals.

Seed-Based FC Analysis

In each individual rsfMRI data analysis, the hypothalamic region was defined according to a previous study (Baroncini et al., 2012). This provided a comprehensive atlas comparing anatomical, histological and MR images of the human hypothalamus and transferred each identified structure to the MNI space. The seed point was selected as (2, −1, −12) and was located in the PVN, which releases CRH and AVP. Seed spheres were constructed by drawing a 6-mm radius sphere around the seed point, with a time series for the seed sphere extracted from the preprocessed data. Seed-based rsFC analysis was performed using the temporal correlation approach. Time series were averaged across all voxels within each seed's sphere. Pearson's correlation analysis was performed between the seeds and the remaining voxels. The resulting values were transformed to Z values to improve their Gaussian distribution.

Statistical Analysis

To explore the rsFC differences between the groups in the MNI standard space, second-level random effect two-sample *t*-tests, with the GMVs as covariates, were performed on the individual normalized FC maps in a voxel-by-voxel manner. AlphaSim, a program based on Monte Carlo simulations and implemented by Analysis of Functional NeuroImages (AFNI)[4], was used to correct for multiple comparisons. Monte Carlo simulations determine the random distribution of the cluster size for a given per voxel threshold (Ledberg et al., 1998). According to this distribution, the statistical threshold was set at $P < 0.05$ and a cluster size >198 voxels, which corresponded to a corrected $P < 0.05$. The correction was confined within the GM mask and was determined by Monte Carlo simulations (Ledberg et al., 1998).

Pearson's Correlation Analysis of Hypothalamic FC

To determine whether the rsFC of the hypothalamus showed significant group differences that were correlated with the clinical variables, Pearson's correlation analyses were performed between the Z-values from the abnormal brain regions and the clinical parameters of the D-AD and nD-AD patients in a voxelwise manner. The statistical threshold was set at $P < 0.05$ (after false discovery rate (FDR) correction; Ellis et al., 2000).

RESULTS

Demographics and Clinical Characteristics

Overall, there were 22 AD patients in the D-AD group and 21 AD patients in the nD-AD group. The D-AD and nD-AD groups were well matched in terms of age ($t = -1.414$, $P = 0.165$), sex distribution ($\chi^2 = 0.024$, $P = 1.000$), and years of education ($t = 0.757$, $P = 0.453$). None of the patients were excluded according to our exclusion criteria. There was a significant difference in the HAMD-17 scores between the two groups ($t = 14.253$, $P < 0.001$). Details of the demographic data and corresponding tests are shown in **Table 1**.

GM Volume

We found no whole brain GMV differences between the nD-AD patients and D-AD patients (two-tailed *t*-test, $t = -0.5898$, $P = 0.5586$).

[1]http://www.fil.ion.ucl.ac.uk/spm
[2]http://www.bic.mni.mcgill.ca
[3]http://www.restfmri.net
[4]http://afni.nimh.nih.gov

TABLE 1 | Demographic and neuropsychological data.

	D-AD	nD-AD	t/χ^2	*p*
Gender, *n* (M/F)	22 (11/11)	21 (11/10)	0.024	1.000
Age, years	71.9 ± 4.5	73.9 ± 5.2	−1.414	0.165
Education, years	9.7 ± 2.2	9.1 ± 2.4	0.757	0.453
MMSE	20.9 ± 2.3	20.4 ± 1.7	0.787	0.436
HAMD	13.1 ± 2.4	3.8 ± 1.6	14.258	0.000
D-NPI	6.00 ± 1.6	0	–	–

Data represent mean ± SD. Data were analyzed using independent sample t-tests. AD, Alzheimer's disease; D-AD, Alzheimer's disease patients with depressive symptoms; nD-AD, non-depressed AD patients; M, male; F, female; MMSE, Mini-Mental State Examination. D-NPI, depression domain of the Neuropsychiatric Inventory; HAMD, Hamilton Depression Rating Scale.

Abnormal Regional Brain Dysconnectivity Pattern in D-AD Patients

The results of the two-sample *t*-tests showed significant rsFC alterations in the related brain regions of the D-AD patients compared with the nD-AD patients ($P < 0.05$, AlphaSim corrected; **Table 2**). Specifically, we found that the D-AD patients exhibited decreased FC values, with peak differences in the right middle temporal lobe and the right superior temporal lobe (**Figure 1**, **Table 2**). All results were shown in the MNI template.

Correlation between Hypothalamic FC and Neuropsychological Performance

No correlation was found between the MMSE, NPI, or HAMD scores and the hypothalamic FC in the nD-AD or the D-AD patients.

DISCUSSION

We used rsFC to examine the FC between the hypothalamus and the whole brain in AD patients. We found that, compared with the nD-AD patients, the D-AD patients exhibited reduced FC among the hypothalamus, the right middle temporal gyrus (MTG) and the right superior temporal gyrus (STG), suggesting that abnormal FC between the hypothalamus and the temporal lobe plays a key role in the pathophysiology of depression in AD patients. To the best of our knowledge, this is the first rsfMRI report showing disrupted hypothalamic FC in D-AD patients.

The evidence suggests that limbic-cortical-striato-pallido-thalamic structures organize emotional expression. Dysfunction within and between the structures in this circuit may induce disturbances in emotional behavior and in other cognitive aspects of the depressive syndrome in humans (Sheline, 2003; Drevets et al., 2008; Terroni et al., 2011). Lu et al. (2016) reported that first-episode, untreated MDD patients show significant volume reductions in the thalamus, while probabilistic tractography found that the deformed thalamic shape area had connections with the frontal and temporal lobes, which were related to major depression. Because limbic structures enable forebrain modulation of the hypothalamus and brainstem, their dysfunction can account for disturbances in autonomic regulation and neuroendocrine responses that are associated with mood disorders (Maletic et al., 2007). Several brain regions (including the temporal lobe) regulate emotional responses as circumstances and are known as top-down cognitive control mechanisms. Recent research suggests that reappraisal, a top-down emotion regulation strategy, is more effective in decreasing self-reported negative affect when emotions are generated in a top-down, vs. bottom-up manner (Otto et al., 2014; Morawetz et al., 2016). A few studies have shown GM abnormalities in the temporal cortex in treatment-resistant depression (TRD), treatment-responsive depression (TSD) and late-life depression (LLD) patients. Further, based on FC analysis using the right MTG as the seed, both the TRD and TSD patients show altered connectivity, mainly in the default-mode network (Ma et al., 2012; Harada et al., 2016). Studies of antidepressant treatment of LLD also showed that remission status is associated with right MTG changes (Khalaf et al., 2016; Karim et al., 2017).

Reduced FC between the hypothalamus and the temporal lobe has also been shown to promote the release of CRH due to abnormal inhibitory connections. The subsequent result is raised plasma adrenocorticotropic hormone levels, which in turn increase the number of GM lesions in the temporal lobe (Bennett, 2011). Based on animal experiments, Myers et al. (2016) confirmed that the hypothalamus represents an important stress-integration center, regulating behavioral processes and connecting the limbic forebrain to the neuroendocrine system. Moreover, the hypothalamus appears to be uniquely situated to play a role in stress-related pathologies associated with limbic-hypothalamic dysfunction. Dysfunction of the limbic-HPA (LHPA) system results from higher ACTH levels and

TABLE 2 | Brain regions with significantly decreased functional connectivity (FC) values in the D-AD group compared with the nD-AD group.

Brain region	Voxels	BA	MNI coordinates			*T* value
			x	*y*	*z*	
Right middle temporal lobe	293	21	57	−36	3	−3.1523
Right superior temporal lobe		22	50	−21	8	

D-AD, AD patients with depressive symptoms; nD-AD, non-depressed AD patients; BA, Brodmann's area; MNI, Montreal Neurological Institute.

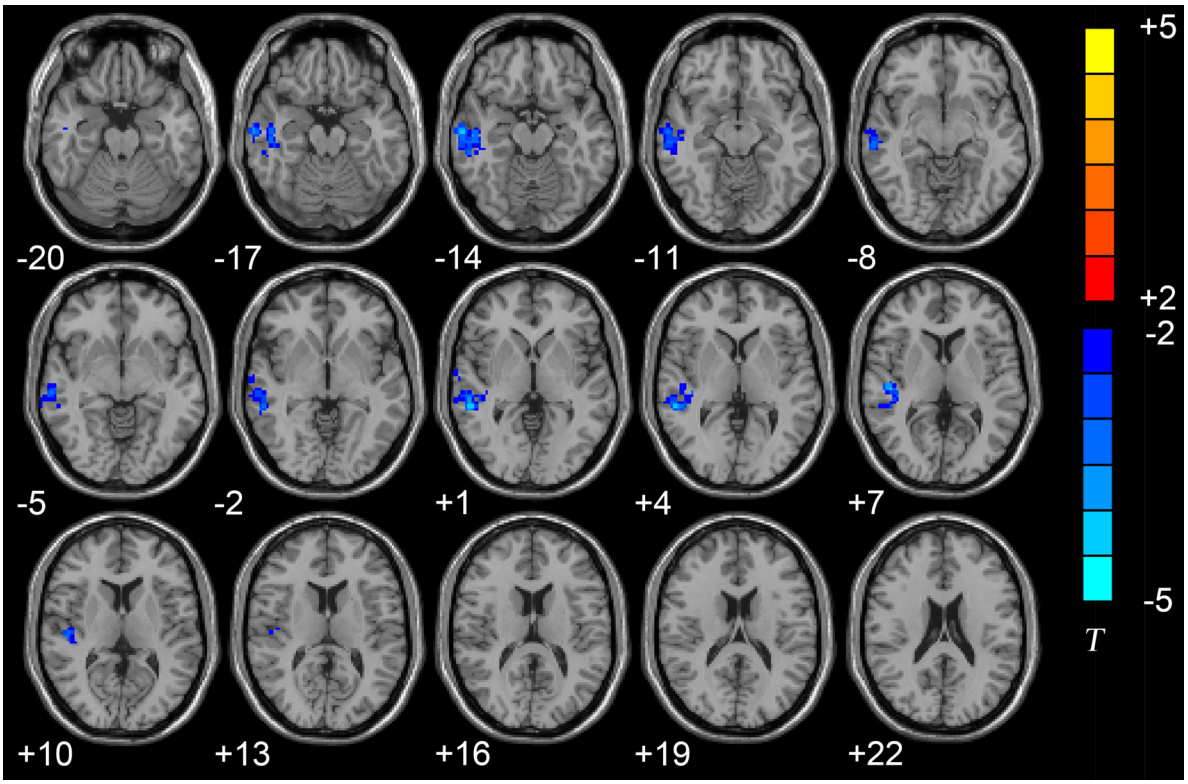

FIGURE 1 | Axial brain region maps showing the decreased functional connectivity (FC) values in the depressed AD patients (D-AD) group compared with the non-depressed AD patients (nD-AD) group ($P < 0.05$, AlphaSim corrected). Results were viewed on the Montreal Neurological Institute (MNI) T1 template and the T-value scale is shown on the right of the image.

contributes to disturbances in serotonergic and noradrenergic neurotransmission (Twardowska and Rybakowski, 1996). Coexistent dysregulation of the LHPA is predominantly linked to glucocorticoid receptor (GR) dysfunction within the limbic system. Along with hypercortisolemia, an imbalance of mineralocorticoid receptors (MR) and GR results in impaired negative feedback mechanisms in the LHPA loop. Impaired GR function and an MR/GR imbalance alters the negative feedback regulation within the LHPA, followed by the dysregulation and hypercortisolemia that is associated with decreased postsynaptic 5-HT1A receptor activity, thereby resulting in serotoninergic dysfunction (Lesch et al., 1990).

The MTG is located in the extended dorsal attention system and is involved in cued attention and working memory (Corbetta and Shulman, 2002; Fox et al., 2006). Using an optimized voxel-based method, Peng et al. (2011) reported reduced GMV in the bilateral MTG in a group of first-episode MDD patients. In addition, Wu et al. (2011) reported that TRD patients show higher regional homogeneity in the right MTG than those of treatment non-resistant depression patients and healthy controls. Moreover, lower amplitude low-frequency fluctuation values in this region were found to be reduced in both TRD and TSD patients (Guo et al., 2012). These findings suggest that the MTG is part of a relevant functional network associated with MDD.

The STG consists of the primary auditory cortex and the auditory association areas (Pearlson, 1997; Kim et al., 2000; Hou et al., 2016) and has been implicated in emotional processing and social cognition (Allison et al., 2000; Arnsten and Rubia, 2012). A recent meta-analysis of fMRI studies of MDD noted that the STG is one of the most consistently identified regions involved in its pathophysiology (Fitzgerald et al., 2008). Takahashi et al. (2010) delineated STG subregions (namely, the planum polare, planum temporale, rostral STG, caudal STG and Heschl's gyrus) and the temporal pole using MRI in 29 currently depressed patients, 27 remitted depressed patients, and 33 age- and gender-matched healthy control subjects. Both the current and remitted MDD patients showed significant volume reductions in the left planum temporale and the bilateral caudal STG compared with healthy controls. Guo et al. (2011) used a regional homogeneity approach to explore the brain activity features of TRD patients. Compared with healthy controls, decreased regional homogeneity was found in the TRD patients in the left insula, STG, inferior frontal gyrus, lingual gyrus and anterior cerebellar lobe. Our finding showing reduced FC between the hypothalamus and the STG in D-AD patients is consistent with those of previous studies, suggesting that abnormal STG activity may be associated with negative emotional processing.

Several limitations should be considered when interpreting our results. First, the hypothalamus encompasses a relatively

small volume; thus, the accuracy of the seed point location depends on the spatial resolution of the fMRI images and the accuracy of the registration method. Higher spatial resolution fMRI images and a higher accuracy registration method should be used to improve the accuracy of the seed point location (Klein et al., 2009; Yacoub et al., 2015). Second, a group of MDD patients should be included in future studies. Comparisons between MDD and D-AD patients can provide more information regarding the pathophysiology of depression in AD patients. Third, in this study, in consideration of the dysregulation of the HPA-axis involved in both MDD and AD (Sudheimer et al., 2015) and the critical role of the PVN in the dysregulation of the HPA-axis, we choose the PVN as the seed point for the FC analyses of the whole brain. Meanwhile, both the AVP and CRH released by the HPA-axis contribute to the signs and symptoms of depression; thus, detecting the hormone concentrations of AVP, CRH and ACTH will be one of our future studies. Third, we used a relatively small sample; therefore, our statistical power was low and limited. Future studies should use a larger sample size to increase the statistical power. Finally, there are issues of the sample, where they were not matched on body weight or Body Mass Index, which may be one of the factors that can affect the brain function network in AD patients (Sugimoto et al., 2017).

CONCLUSION

Here, we used rsfMRI and rsFC analysis to examine the intrinsic dysconnectivity patterns of the hypothalamus in both D-AD and nD-AD patients. We found decreased FC in the right middle temporal lobe and the right superior temporal lobe. These findings enhanced our understanding of hypothalamic dysfunction in D-AD patients.

AUTHOR CONTRIBUTIONS

XL was responsible for data acquisition and analysis, and drafting of the manuscript. ZG, XH and WC were responsible for design/conception of the study, and data acquisition and analysis. GB and YT was responsible for drafting the manuscript and critical revision of the manuscript for intellectual content. HH was responsible for data acquisition and analysis. WC and XC were responsible for analysis and interpretation of the data. All authors agree to be accountable for all aspects of the work.

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Indication of Cognitive Change and Associated Risk Factor after Thoracic Surgery in the Elderly: A Pilot Study

Kay Kulason[1], Rui Nouchi[1,2,3], Yasushi Hoshikawa[4,5], Masafumi Noda[5], Yoshinori Okada[5] and Ryuta Kawashima[1,6]*

[1] Department of Advanced Brain Science, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, [2] Creative Interdisciplinary Research Division, Frontier Research Institute for Interdisciplinary Science, Tohoku University, Sendai, Japan, [3] Human and Social Response Research Division, International Research Institute of Disaster Science, Tohoku University, Sendai, Japan, [4] Department of Thoracic Surgery, School of Medicine, Fujita Health University, Toyoake, Japan, [5] Department of Thoracic Surgery, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan, [6] Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

Background: This pilot study investigated the effects of partial pulmonary lobectomy lung surgery on cognitive functions of elderly Japanese patients. It is recognized that elderly patients undergoing surgery have increased risk of Postoperative Cognitive Decline (POCD), a condition in which learning, memory, and processing speed is greatly reduced after surgery. Since elderly patients are more likely to exhibit symptoms of POCD, the incidence is increasing as the population receiving surgery is aging.

Methods: Cognitive function was measured for all subjects ($n = 12$) before and after surgery using three different cognitive tests: Mini-Mental Status Exam-Japanese (MMSE-J), Frontal Assessment Battery (FAB), and a computerized Cogstate Brief Battery (CBB). Changes in these measures indicate changes in cognitive function. In addition, the 12-item General Health Questionnaire (GHQ-12), the Geriatric Depression Scale (GDS), and the 5-item Quality of Life questionnaire (QOL-5) were administered at each time point to measure mental and emotional state. Changes in outcome measures were analyzed via Wilcoxon signed-rank test. Exploratory correlation analysis was conducted using Spearman's rho.

Results: Data show a decline in detection (DET; $p = 0.045$) and identification (IDN; $p = 0.038$). Spearman's correlation coefficient show a significant correlation between postoperative DET scores and postoperative IDN scores ($\rho = 0.78$, $p = 0.005$), a significant correlation between change in IDN and baseline GHQ-12 scores ($\rho = -0.595$, $p = 0.027$), and a significant correlation between change in one-back (OBK) scores and duration of anesthesia ($\rho = -0.72$, $p = 0.012$).

Discussion: This was the first report to examine cognitive decline after major thoracic surgery in Japanese patients. Previous studies have evidenced that POCD is a common phenomenon after surgery, and that age is a major risk factor. The CCB measured significant change in two cognitive domains: attention and psycomotor function. This study clarified that decline in cognition is detectable in certain measures after thoracic

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Shunsuke Tachibana, Sapporo Medical University, Japan

***Correspondence:**
Rui Nouchi
rui.nouchi.a4@tohoku.ac.jp

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surgery in the elderly Japanese patient population. Additionally, longer anesthetic exposure may negatively impact attention and working memory, and preoperative mental wellbeing is a possible predictor of POCD. These preliminary results have important implications and support the need for future studies.

Keywords: POCD, mental health, GHQ, prevent, cognitive decline, thoracic

INTRODUCTION

Symptoms including memory loss and lack of concentration often occur in patients who have undergone surgery (Bedford, 1955). Although not officially diagnosed, these symptoms are part of a condition called postoperative cognitive decline (POCD) (Tsai et al., 2010) and is often described in literature as acute (1 week), intermediate (3 months), and long-term (1+ years) (Leung and Sands, 2009). POCD has been reported in the literature since the 1950s, and recent studies suggest that anesthesia is a potential culprit (Bedford, 1955; Stratmann, 2011). Bedford (1955) published a retrospective review of 1193 elderly patients who, over a 5-year period, underwent surgery with general anesthesia. The review concluded that cognitive problems correlated with anesthetic agents and hypotension, and that 'operations on elderly people should be confined to unequivocally necessary cases.' Separately, an international multicenter study on POCD reported memory impairments in 26% of patients 60 years and older. Deficits in cognitive functions were reported to last anywhere from months to years (Moller et al., 1998). While most incidents of POCD naturally recover 6 months after surgery, in nearly 2% of POCD cases symptoms can last until death (Bedford, 1955). POCD is also a problem as it is also strongly associated with premature departure from the labor market (Steinmetz et al., 2009). Furthermore, people with POCD are at higher risk of death within the first year after surgery (Monk and Price, 2011).

In fact, studies assessing general health and quality of life have found that changes in cognitive function are correlated with physical health, emotional health, and quality of life (Launer et al., 1995; Benito-León et al., 2002; Colcombe and Kramer, 2003; Hopkins et al., 2004). A decline in quality of life and general health are associated with declines in cognitive functions and depression (Lindholt et al., 2002; Jones et al., 2006). Interestingly, associations between change in test performance and age, physical disability, and a number of depressive symptoms have been reported (Stockton et al., 2000). Preoperative symptoms of depression have also been associated with the development of postoperative delirium (Leung et al., 2011). Although POCD and delirium are believed to be separate entities, their symptoms are similar and their relationship has yet to be determined (Deiner and Silverstein, 2009; Tsai et al., 2010). Age is nevertheless the biggest risk factor for POCD (Moller et al., 1998; Monk et al., 2008). Over the past 20 years, the number of older people undergoing surgical procedures has increased faster than the population is aging (Etzioni et al., 2003; Sauër et al., 2009). Consequently, maintaining and preventing cognitive decline in older adults after surgery is drawing increasing attention (Schaie et al., 1987; Baltes et al., 1989; Simões, 1998; Ball et al., 2002; Hedden and Gabrieli, 2004; Willis et al., 2006; Bissig and Lustig, 2007; Smith et al., 2009; Tucker-Drob et al., 2009; Zelinski, 2009; Lövdén et al., 2010; Mowszowski et al., 2010; Williams and Kemper, 2010; Martin et al., 2011; Tardif et al., 2011; Fernández-Prado et al., 2012).

Changes in cognitive function in the elderly Japanese population have previously been examined (Saito et al., 2013; Tachibana et al., 2015). Tachibana et al. (2015) focused on the effect of administering desflurane anesthesia vs. sevoflurane anesthesia in all surgeries lasting longer than 4 h. Additionally, Tachibana et al. (2015) measured cognitive function using only the Mini-Mental Status Exam (MMSE) 24h before and after surgery. Saito et al. (2013), on the other hand, examined patients undergoing carotid endarterectomy for ipsilateral cervical internal carotid artery stenosis (≥70%) and analyzed neuropsychiatric data on cognitive function taken preoperatively and 1 month postoperatively with brain proton MR spectroscopy. The main aim of this present study is to examine the cognitive changes after major thoracic surgery and utilizes the MMSE in conjunction with several other measures including a computerized battery to detect changes in cognitive function. Cognitive functions were measured via the conventionally used Mini-Mental Status Exam-Japanese (MMSE-J) and the Frontal Assessment Battery (FAB) in conjunction with the Cogstate Brief Battery (CBB). Additionally, the 12-item General Health Questionnaire (GHQ-12), the Geriatric Depression Scale (GDS), and the 5-item Quality of Life questionnaire (QOL5) were administered at each time point to measure mental and emotional state. Testing for this present study was administered approximately 1 day before surgery and 1 week after surgery.

This study investigated possible risk factors of POCD that could eventually be targeted to reduce the risk of and prevent declines in cognitive functions after surgery. Several studies have investigated POCD risk factors, and they have concluded that age is the largest risk (Salthouse, 1996, 2003; Royall et al., 2004; Coppin et al., 2006; Yakhno et al., 2007). Carrying the APOE4 genotype and inflammation are also believed to be risk factors of POCD. Studies have suggested that the effects of APOE are mediated through alterations in lipid transport in regenerating neurons, proinflammatory cytokine release from activated microglia, amyloid precursor protein metabolism, increased blood brain barrier permeability, alterations in platelet function, and systemic inflammation (Tsuang and Bird, 2002; Parihar and Hemnani, 2004; Moretti et al., 2005). Unfortunately, carrying the APOE4 gene and inflammation are not factors that can be easily treated or prevented. Moreover, anesthesia alone has been shown to increase the level of proinflammatory cytokines (Cao et al., 2012; Wu et al., 2012; Žura et al., 2012). Additionally, depression has been linked with cognitive decline. A review of

TABLE 1 | Demographic information.

Gender	5 males, 6 females
Mean Age (years)	70.16 ± 6.07
Race/Ethnicity	Japanese
Procedure	Partial pulmonary lobectomy
Location of procedure	Tohoku University Hospital
Mean anesthesia duration (min)	257.45 ± 70.14
Mean anesthesia administered	
−Remifentanil (mg)	4.31 ± 2.47
−Fentanyl (mg)	0.28 ± 0.13

a decade of the literature concluded that major depression has been associated with impaired cognitive functioning (Hammar and Årdal, 2009). Therefore, it was hypothesized that time under anesthesia and preoperative depressive symptoms would correlate with cognitive decline.

MATERIALS AND METHODS

Participants

A total of 12 volunteers (six males, six females) were recruited from respiratory patients undergoing lung surgery with general anesthesia. Participant demographics are noted in **Table 1**. Respiratory patients who underwent partial pulmonary lobectomy lung surgery to remove tumor growths were recruited from Tohoku University Hospital. A doctor of thoracic surgery from the Tohoku University Hospital referred participants to the study. Participants were native Japanese speakers who self-reported to be right-handed and were 60 years and older (mean age 70.16 ± 6.07 years). Participants were unconcerned with their memory functions.

Patients admitted into the hospital were informed about the study prior to surgery. Interested patients received both a written and a verbal explanation of the study. Prior to participating in the study, all subjects were requested to sign the informed consent form. The protocol of the study and the consent form were approved by the Ethics Committee of Tohoku University Graduate School of Medicine. This study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN000019832).

Cognitive Function Measures

A total of three cognitive tests were administered to participants before (1 day) and after surgery (∼1 week, 5–17 days between assessment). The Mini-Mental State Examination-Japanese (MMSE-J) was administered to the participants after receiving consent. The MMSE-J is a 30-point cognitive test used extensively in both the clinical and research settings to measure cognitive impairment (Pangman et al., 2000). Conventionally, clinicians consider a person's MMSE-J score along with their history, a physical health exam, symptoms, and results from other tests to assess Dementia. A higher MMSE-J score indicates better cognitive performance. The MMSE is the most common mental status test used to determine POCD (Folstein et al., 1975; Tombaugh and McIntyre, 1992; Wang et al., 2014). For test–retest intervals of 2 months or less, the MMSE has been shown to have good reliability (Folstein et al., 1975; Helkala et al., 2002).

Following the MMSE-J, the participants were administered the Frontal Assessment Battery (FAB). The FAB is an 18-point cognitive test that is commonly performed at bedside or in a clinical setting to help measure cognitive impairment in executive functions (Dubois et al., 2000; Kugo et al., 2007; Nakaaki et al., 2007). Again, higher scores indicate better performance. The Japanese translation of the FAB has previously been shown to be comparable to the original English versions and has a good test-retest reliability at 3-weeks (Kugo et al., 2007; Nakaaki et al., 2007). Both the MMSE and FAB are commonly administered in studies determining cognitive decline (Brown et al., 2010; Bugalho et al., 2013; Barulli et al., 2015).

After the FAB, participants were tested using a laptop running CBB to measure the speed of processing, visual attention, visual learning and memory, and attention and working memory. This computerized battery has been shown to effectively determine cognitive decline (Maruff et al., 2009, 2013; Sauër et al., 2009; Brown et al., 2010; Lim et al., 2012) and has also been shown to be effective in Japan (Yoshida et al., 2011). Previous studies on the test-retest reliability of the CBB have indicated that there are no retest-related increases in scores after 1 month. However, the retest scores have been shown to increase at 1-week or less (Maruff et al., 2009, 2013; Lim et al., 2012). The four CBB tasks have previously been described in detail (Collie et al., 2002; Falleti et al., 2006; Maruff et al., 2013) and are summarized here.

A single playing card is presented in the center of the computer monitor for each trial of each of the four tasks. The values, color, and suit of the playing cards were determined by the requirements of each task. For each of the four tasks, participants were required to respond either "Yes" or "No" by pressing the "K" (yes) or "D" (no) key on the keyboard as quickly and accurately as possible. While the "K" and "D" keys were specifically identified to the participants, the keys surrounding "K" (e.g., U, I, O, J, L, M, ",", ".") and "D" (e.g., W, E, R, S, F, X, C, V) also recorded responses during the task. At the beginning of each task, task rules were presented on the computer monitor and were also explained verbally to the participant. This was followed by an interactive demonstration in which participants practiced the task. After completing the practice trial, the participant was again reminded of the task question and started the recorded, full-length task. For each of the four tasks, the reaction time and accuracy were recorded and expressed as mean reaction time (in milliseconds) and accuracy (proportion correct). Cogstate has selected a single representative performance measure for each task on the basis that it comes with a normal data distribution, has no floor or ceiling effects, does not have restricted range, and has good reliability, stability, and sensitivity to change (Fredrickson et al., 2010; Hammers et al., 2011). Each of the four tasks from the CBB is described in order below. The four tasks were always presented in the same order.

The Detection (DET) task measures psychomotor function by recording reaction times. The participant was required to attend to the card in the center of the screen and respond to the question: "Has the card turned over?" Participants were instructed to press

the "Yes" key as soon as the card turned face up to reveal a generic joker card. The same joker card was presented in each trial. The task ended after 35 correct trials. The primary performance measure for this task was reaction time in milliseconds (speed), which was normalized using a $\log_{10}$ transformation. A lower score indicates better performance. The sign was changed when calculating change in score so that a greater negative change indicates worse performance postoperatively.

The Identification (IDN) task is a choice reaction time test measures visual attention. The participant must attend to the card in the center of the screen and respond to the question "Is the card red?" by pressing the "Yes" and "No" buttons. The face of the displayed cards was either red or black jokers in equivalent numbers which appeared in random order. These joker cards were different to that of the joker displayed in the DET task. The task ends after 30 correct trials. Anticipatory responses were excluded, and another trial was given so that all participants completed the 30 trials. The primary performance measure was reaction time in milliseconds (speed), which was normalized using a $\log_{10}$ transformation. A lower score indicates better performance. The sign was changed when calculating change in score so that a greater negative change indicates worse performance postoperatively.

The One Card Learning (OCL) task is a continuous visual recognition learning task that assesses visual learning within a pattern separation model (Yassa et al., 2010). Theoretical models of pattern separation model specify that information is organized in orthogonal and distinct non-overlapping representations so that the memories can be stored rapidly without interference (Norman and O'Reilly, 2003). The task requires the participant to attend the card in the center of the screen and respond to the question "have you seen this card before in this task?" using the "Yes" and "No" buttons. Playing cards numbered from 1 and 13, minus face-cards, were displayed. Six cards are drawn at random from the deck and repeated throughout the task. These cards are interspersed with distractor cards (non-repeating cards). The task ends after 80 trials, which do not reschedule for post-anticipatory correct trials. The primary performance measure for this task was the proportion of correct answers (accuracy), which was normalized using an arcsine square-root transformation. A lower score indicates worse performance, therefore a greater negative change in score after surgery indicates worse performance postoperatively.

The One-Back (OBK) task is a task of working memory and attention. The participants must attend to the card in the center of the screen and respond to the question "is the card the same as that on the immediately previous trial?" using the "Yes" and "No" buttons. The same deck of cards from the OCL task is used. The task ends after 30 correct trials. Correct but post-anticipatory responses led to the scheduling of an extra trial. The primary performance measure for this task was the proportion of correct answers (accuracy), which was normalized using an arcsine square-root transformation. A lower score indicates worse performance, therefore a greater negative change in score after surgery indicates worse performance postoperatively.

A series of integrity checks can be applied to the CBB data to ensure that each subject is completing each task properly. For instance, it is expected that the subject performs the quickest on the easiest task (i.e., Detection). It is also expected that accuracy is above chance level for the results to be considered real. For example, if a person performs below 50% accuracy on a task with a choice of 2 responses, they are performing at chance level. As a result, it is impossible to know whether the subject understood the task.

Psychological Questionnaires

In addition to the above cognitive measures, the GHQ-12, GDS, and QOL-5 were administered immediately after the cognitive assessments before and after surgery to measure mental and emotional state. The GHQ-12 is a self-report measure of psychological morbidity that screens the domains of depression, anxiety, somatic symptoms and social withdrawal. It is routinely used as a unidimensional measure to detect psychiatric disorders. It is widely used in clinical practice (Richardson et al., 2007), epidemiological research (Henkel et al., 2003), and psychological research (Jones et al., 2006). The GHQ-12 consists of six items that are positive descriptions of mood states and six that are negative descriptions of mood states. The questionnaire is structured so that a higher score is an indication that the individual is at higher risk for developing a psychiatric disorder.

The GDS is a self-report measure designed specifically to screen for depression in the elderly population. This short screening measure is geared toward the cognitive and emotional symptoms of depression including feelings of worthlessness, preference for staying at home, and concern about memory problems. The GDS consists of 30 questions in a simple yes/no format. Of the 30 questions, 20 of the questions indicate the presence of depression when answered positively, while the remaining 10 questions indicate the presence of depression when answered negatively (Yesavage et al., 1982–1983).

The QOL-5 is a self-report measure for global and generic quality of life. This 5-item questionnaire has been shown to have internal consistency and sensitivity, and relevant and practical outcome measurement is available for clinical databases (Lindholt et al., 2002). All tests were administered and scored by trained project investigators. The type of general anesthesia administered, the amount of anesthesia administered, the anesthesia duration, the surgery duration, age, and sex were noted.

Statistical Analysis

This study was designed to determine whether there is a decline in cognition after surgery in elderly lung surgery patients. Before conducting all statistical analysis, we checked gender differences in all tests using Mann–Whitney *U*-test. Change in scores was calculated (post – pre) for each outcome measure. The sign for the change in score of DET and IDN were reversed so that negative numbers reflected poorer performance. In order to compare cognitive function before and after surgery for all participants, we employed a Wilcoxon signed-rank test. This determined whether cognitive functions declined post-surgery. Additionally, Spearman's correlation coefficients were used to examine correlations between test scores and covariates including questionnaire scores, the amount of anesthesia administered,

and duration of surgery. The level of significance was set at $p < 0.05$. One participant was removed from analysis for failing three of the five CBB integrity checks of the two testing sessions. Statistical analysis was conducted using RStudio (version 3.2.4 [2016-03-10]).

RESULTS

There were no significant differences in all test scores between genders at both baseline and follow-up. Participants scored similarly on all outcome measures at baseline, and significant changes were detected for two CBB cognitive domain measures post-surgery—the IDN and DET scores (**Table 2**). In a separate representation of the data, changes in cognitive test outcome measures for each subject are listed in **Table 3**. One subject was removed from analysis for failing 3 CBB integrity checks over the two sessions, which indicated a lack of understanding of the task, or not completing the task seriously. Differences between pre-surgery and post-surgery scores were analyzed via Wilcoxon signed-rank tests. Data show a decline in DET ($p = 0.045$) and IDN ($p = 0.038$, **Table 2**). While some individuals have a positive change in their DET and IDN scores post-surgery from baseline, the overall trend of the group is a decline in DET and IDN (**Table 3**). No significant changes were apparent in the other test score outcome measures. Data does not indicate that there is a global decline in cognitive functions after thoracic surgery. Additionally, Spearman's correlation coefficient indicates a significant relationship between postoperative DET scores and postoperative IDN scores ($\rho = 0.78$, $p = 0.005$, Supplementary Table 2). There are no significant correlation between age and change in DET, nor is there a significant correlation between age and change in IDN (Supplementary Table 1).

Spearman's correlation coefficient also indicates a significant relationship between the change in IDN scores and baseline GHQ-12 scores ($\rho = -0.595$, $p = 0.027$; **Figure 1A**). Higher GHQ-12 scores were associated with greater IDN score declines after thoracic surgery. No other significant correlations were apparent between change in test scores and baseline questionnaire scores (Supplementary Table 1). Additionally, change in OBK scores were significantly correlated with anesthetic duration ($\rho = -0.72$, $p = 0.012$; **Figure 1B** and Supplementary Table 1). The longer the duration of anesthesia, the greater the decline in OBK score after surgery. A greater negative change in OBK indicates a decline in attention and working memory cognitive function as measured by the OBK task.

DISCUSSION

This pilot study was designed to investigate possible, and potentially treatable, risk factors of cognitive decline after major surgery in the elderly Japanese patient population. As previously mentioned, age has been indicated as a major risk factor for POCD and is found in approximately 26% of individuals over 60 years old (Moller et al., 1998). This was the first study to investigate the correlation between depressive symptoms and cognitive decline after surgery. Additionally, it was the first study to examine the effects of thoracic surgery on cognitive functions for the Japanese elderly population.

Preliminary results revealed a decline in both DET and IDN scores after surgery. Previous studies on the test–retest reliability of the CBB have indicated that there are no retest-related increases in score with 1-month intervals. However, at 1-week intervals, the second test scores have been shown to slightly increase (Falleti et al., 2006; Hammers et al., 2011). Despite this fact, our data showed significantly lower DET and IDN scores after surgery compared to baseline. The decline in these scores, especially with the expected increase in scores 1-week post-surgery due to test-retest effects, supports the hypothesis that there is a cognitive decline after thoracic surgery. In fact, this cognitive decline is likely POCD since previous studied regarding POCD have found changes in both attention and processing speed (Tsai et al., 2010)—the same declines indicated by our current data. Nevertheless, a clear conclusion cannot be drawn due to the large SD in our present data for this pilot study, and the small number of subjects. Continued investigations are necessary to determine if POCD is detectable in the elderly thoracic surgery population using the CBB.

There was also a significant correlation between postoperative DET scores and postoperative IDN scores. After surgery, there were significant declines in both DET scores and IDN scores, so there may be a common mechanism that underlie these declines. This may be the case because the task measuring psychomotor function (DET) and visual attention (IDN) share the component of processing speed in that the participant is tasked with responding as quickly as possible in both tasks.

Additionally, Spearman's correlation coefficient identified a significant correlation between the decline in IDN and baseline GHQ-12 scores. The mental well-being of the patient prior to surgery is potentially a predictor of POCD. Previous studies have found associations between a decline in cognitive function and declines in health and quality of life (Launer et al., 1995; Benito-León et al., 2002; Colcombe and Kramer, 2003; Hopkins et al., 2004). A study conducted by Leung et al. (2005) concluded that preoperative depression was a risk factor for delirium. Delirium is an acute state of disorientation that is characterized by disturbances in attention and awareness. Symptoms include hallucinations and inappropriate communication and/or behavior. In contrast, patients with POCD are oriented, but exhibit declines in one or more neuropsychological domains. Both delirium and POCD feature deficits in attention, so some believe that the phenomena are on the same spectrum and that delirium is a higher grade of POCD (Inouye et al., 1990; Rudolph et al., 2008). Nevertheless, whether they are related events on a continuum, or whether they are distinct events remain unclear. Should the events be related, it would make sense that the results of this study indicate that preoperative GHQ-12 scores are significantly correlated with change in IDN. The finding adds further support to Leung et al.'s (2005) conclusion that preoperative depression is a risk factor for the events on this spectrum. In addition, as noted above, previous findings have

TABLE 2 | Primary outcome measure scores.

Primary Outcome Measure	Pre-surgery Baseline Scores Mean (±SD)	Pre-surgery Baseline Score Range	Post-surgery Follow-up Scores Mean (±SD)	Post-Surgery Follow-up Score Range	Between score *p*-value
MMSE	27.50 (±1.17)	26–29	27.92 (±1.88)	26–30	0.144
FAB	13.25 (±1.92)	11–16	13.00 (±1.41)	11–15	0.209
DET	86.17 (±12.08)	65–107	93.08 (±7.17)	84–103	0.045*
IDN	96.58 (±6.54)	83–104	99.75 (±3.70)	94–104	0.038*
OCL	99.75 (±3.60)	94–107	99.00 (±5.74)	89–106	0.347
OBK	101.83 (±5.02)	95–107	102.58 (±7.14)	94–116	0.311
GHQ12	3.25 (±2.83)	0–7	3.17 (±3.07)	0–9	0.452
GDS	4.17 (±3.51)	1–8	3.75 (±3.57)	0–6	0.130
QOL5	13.17 (±4.75)	6–19	14.67 (±4.62)	9–21	0.224

*DET and IDN measure reaction time in milliseconds, so higher scores indicate poorer performance. The OCL and OBK measures accuracy, and the MMSE and FAB scoring methods add points for every correct response. Therefore, higher scores indicate better performance. As for the health questionnaire, a higher GHQ12 score indicates poorer overall psychiatric health, while higher scores for GDS and QOL5 indicate better psychiatric health. Wilcoxon signed-rank tests analyzed for differences between Pre-surgery and Post-surgery scores. There was a significant decline in post-surgery DET ($p = 0.045$) and IDN ($p = 0.038$) scores compared to baseline. *Indicates significant difference between pre-surgery and post-surgery score ($p < 0.05$).*

TABLE 3 | Individual and mean (±SD) change in cognitive test scores (post-pre).

ID	ΔMMSE	ΔFAB	ΔDET	ΔIDN	ΔOCL	ΔOBK
sub1	0	1	−18	−2	−4	0
sub2	2	1	−22	−8	6	2
sub3	3	1	−7	−2	−6	−6
sub4	1	−2	4	0	1	4
sub5	0	−2	−5	1	−7	3
sub6	2	−1	−5	−2	9	9
sub7	0	0	10	4	1	0
sub8	1	1	5	1	5	−9
sub9	−1	−1	−28	−19	−1	0
sub10	0	0	−15	−5	−11	−3
sub12	−4	3	3	−3	−3	0
Mean Δ (±SD)	0.36 (±1.86)	0.09 (±1.51)	−7.09 (±12.30)*	−3.18 (±6.15)*	−0.91 (±6.06)	0.00 (±5.56)

*Change in outcome measures was calculated by subtracting the pre-surgery scores from the post-surgery scores. The sign for change in DET and change in IDN were reversed because a lower score indicates better performance for these primary outcome measures. All negative values in this table indicate poorer performance during the post-surgery session. Subject 11 was removed from the analysis. *Indicates significant difference between pre-surgery and post-surgery score ($p < 0.05$).*

indicated that the number of depressive symptoms is associated with changes in test scores and a general decline in cognition (Tsai et al., 2010). The preliminary results of this study indicate a new finding that preoperative mental wellbeing is a predictor of POCD. Therefore, future studies will benefit from gathering more extensive demographic information (i.e., education, marital status, general health).

Interestingly, Spearman's correlation analysis on the data from the present study suggested a significant relationship between change in OBK scores and anesthetic duration. Longer anesthetic exposure was correlated with a greater negative change in OBK score, which indicates a decline in attention and working memory performance after surgery. It has been generally accepted as a rule that the shorter the duration of the anesthetic agent, the shorter the duration of cognitive impairment in the immediate postoperative period. To date, no definitive evidence has been found for the hypothesis that anesthesia itself causes prolonged POCD. Nor is there sufficient evidence to suggest that anesthetics are neurotoxic (Stratmann, 2011). Nevertheless, the present data adds further support to this belief that anesthesia plays a role in POCD.

In addition, there is no significant effect of gender nor of age in the preliminary data. Contrary to present results, population based data has indicated that performance on neurocognitive tests generally decline with age and tend to decline faster in men (Wiederholt et al., 1993). The likely reason is that the small sample size for this pilot study is not enough to examine gender and age effects.

Together, these results suggest that thoracic surgery leads to a decline in cognitive functions related to visual attention and psychomotor functions. Additionally, extended anesthetic duration may have a negative impact on attention and working memory. The data support our hypothesis that cognitive decline after surgery is correlated with time under anesthesia and preoperative emotional health. Therefore, it may be important to work toward reducing the time spent under anesthesia and to

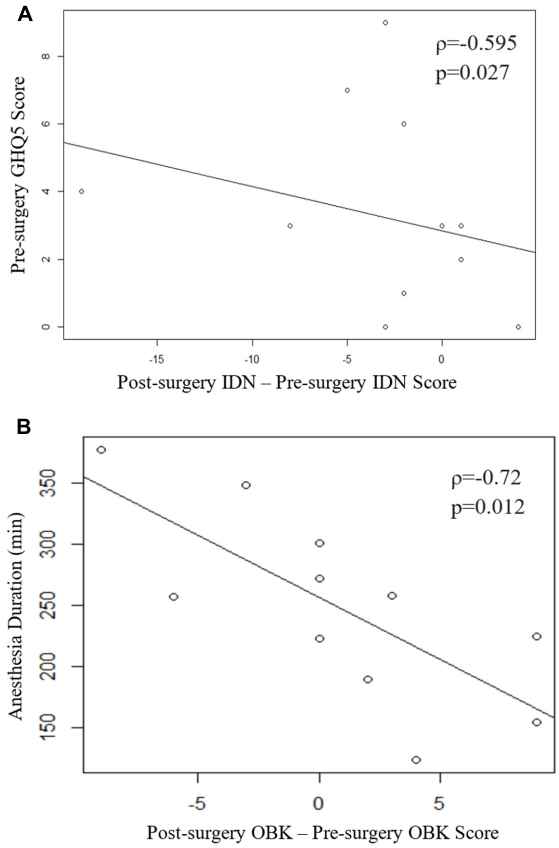

FIGURE 1 | (A) Scatter plot of the change in IDN score vs pre-surgery GHQ-12. Spearman's correlation coefficient indicates a significant relationship ($\rho = -0.595$, $p = 0.027$). **(B)** Scatter plot of the change in OBK scores vs. duration of anesthesia. Spearman's correlation coefficient indicates a significant relationship ($\rho = -0.72$, $p = 0.012$). One subject was removed from analysis for failing 3 of the internal CBB integrity checks over the two sessions.

research the unintended effects of different types of anesthesia on different domains of cognitive function. It may also be important to care for the patient's mental state, in addition to their physical state, to reduce the risk of POCD after surgery.

It is important to consider effects of hypoxia and hypoperfusion on POCD. While hypoxia and hypoperfusion were two of the earliest explanations for postoperative cognitive impairment after surgery, the ISPOCD study examining long-term POCD in the elderly found no statistically significant relationship between hypoxemia or hypotensive episodes and POCD (Moller et al., 1998). Based on the previous study, the hypoxia and hypoperfusion would not affect our results.

This current study does include several limitations. Controlling participant variables (i.e., Excluding those with severe hypertension, Parkinson's disease, multiple sclerosis, thyroid disease, stroke, heart disease, diabetes, utilizing medications that affect cognitive function, etc.) was not realistic due to the short recruitment period. Also, participants were limited to patients receiving thoracic surgery under general anesthesia, and therefore the results are not applicable to all types of surgery. The study should be repeated in patients undergoing different types of surgery of ranging durations using a variety of anesthetics.

Another limitation to consider is the number of participants. Because the recruitment period was short, the number of participants were severely limited. As previously mentioned, the small number of participants made it impossible to employ the same methods used in previous studies in order to detect POCD. However, this was a pilot study intended to detect whether cognitive decline occurs after thoracic surgery in the Japanese elderly population, and to explore the possible effects of cognitive intervention in the elderly population after surgery. Therefore, the small sample size should be enough to provide the basic groundwork necessary to conduct future investigations. Furthermore, a collection of radiological and biochemical data was not feasible for the present study. These data would add strength to the current findings and deepen understanding. Radiological and biochemical data collection should be considered for future studies. In addition, large sample research using the unification of the anesthesia method during surgery is necessary as a proposal for future research.

The most commonly used composite measure to determine POCD is the MMSE. It is used in 21% of studies, according to a review by (Tsai et al., 2010). The majority of these studies have detected a decline in MMSE scores in subjects determined to have POCD. However, it is likely that the present study detected no change in MMSE scores due to test timing. Studies that find changes in MMSE scores after surgery conduct testing immediately after surgery (1–3 days), rather than after 1 week (Tsai et al., 2010). Again, the POCD studies tend to be conducted in patients undergoing cardiac surgery with an older mean age (Tsai et al., 2010). Nevertheless, the results of this study suggest that it is possible to detect declines in two different domains, processing speed and visual attention, 1 week after surgery.

While cognitive functions can be affected by surgery (Moller et al., 1998), most cognitive functions also decrease with age (Hedden and Gabrieli, 2004). Furthermore, people are living longer, and the elderly population is increasing. Just in Japan, 25% of the population is over 65 years of age. This is the highest proportion in the world and represents a 4% increase between 2011 and 2016 (World Bank, 2017). This increase is also reflected in the surgical population. In fact, over the past 20 years, the number of older people undergoing surgical procedures have increased faster than the population is aging (Etzioni et al., 2003). The results of this study have important implications for the need to conduct further work to investigate cognitive decline post-surgery, and the need to explore treatment methods to ameliorate the effects of cognitive decline after surgery, as well as general cognitive decline, in the elderly population.

ETHICS STATEMENT

Ethical approval was provided by the Institutional Review Board of the Tohoku University Graduate School of Medicine

(Ref.2015-1-512). Based on the Declaration of Helsinki, written informed consent was received from each participant.

AUTHOR CONTRIBUTIONS

KK, RN, YH, MN, YO, and RK designed developed the study protocol. KK and RN searched the literature, selected cognitive function measures, created manuals to conduct and rate cognitive measures KK and RN wrote the manuscript with YH, MN, YO, and RK. RK also gave advice related to the study protocol. All authors read and approved the final manuscript. KK and RN contributed equally to this work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2017.00396/full#supplementary-material

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Economic Cognitions Among Older Adults: Parental Socialization Predicts Financial Planning for Retirement

*Francisco Palaci, Irene Jiménez and Gabriela Topa**

Department of Social and Organizational Psychology, Universidad Nacional de Educación a Distancia, Madrid, Spain

Drawing on the model on financial planning for retirement (FPR), the aim of this work is to explore how parental economic socialization both directly and indirectly affects FPR through the mediation of financial literacy, financial planning decisions and financial management. Data from a sample of 280 participants aged between 45 and 63 years were used. The results show that parental economic socialization directly and indirectly influences FPR. Moreover, parental economic behavior acts as a positive model for the development of financial literacy and skills and for decisions about FPR. All the variables increased the explained variance of FPR. Lastly, we discuss the process by which parental economic socialization is positively related to financial literacy and skills that impact on FPR, indicating some implications and future lines of research.

Keywords: aging process, financial cognitions, parental economic socialization, decision-making, financial management behavior

Edited by:
Lia Fernandes,
Universidade do Porto, Portugal

Reviewed by:
Craig Speelman,
Edith Cowan University, Australia
Mª Silveria Agulló Tomás,
Universidad Carlos III de Madrid, Spain

***Correspondence:**
Gabriela Topa
gtopa@psi.uned.es

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INTRODUCTION

We currently live in a time of great economic changes, and the need to save for retirement is determined by the rise in the cost of living in the future and by the augmentation of the older population (Annoni and Weziak-Bialowolska, 2016; Budowski et al., 2016). Increased life expectancy and limited sustainability of public pension system underline that it will be very important to have sufficient economic resources to deal with retirement time (Lytle et al., 2015). Therefore, the appropriateness of individual savings and decisions about investments will be the key to successful aging in contemporary society (Teerawichitchainan and Knodel, 2015). Empirical investigations indicate that parents should take responsibility so their children will improve their levels of financial literacy develop adequate financial behaviors (Jorgensen and Savla, 2010), and learn good economic decision-making. Accordingly, recent research recommends exploring the interaction between parental socialization and financial outcomes under a mediation-based approach (Tang et al., 2015).

This study examines the influence of parental economic socialization on financial planning for retirement (hereafter FPR) and the mediating role of financial literacy, decisions about FPR and financial management, based on the model on FPR of Hershey et al. (2013). Despite the fact that the Hershey's model provides answers to a wide range of present questions about FPR, further exploration of remote antecedents is needed in order to refine our understanding of FPR (Topa et al., submitted). This model states that FPR is determined by three dimensions: capacity, disposition, and opportunities to plan and save, as well as by the interaction that occurs between them.

The first dimension includes the abilities, knowledge and skills that contribute to differences in people's cognitive and intellectual capacity to effectively plan and save for retirement. The second dimension includes the motivational forces and the psychological and emotional factors that determine the likelihood that an individual will begin planning and will sustain the activity over time. Finally, certain external influences, including environmental facilitators and constraints, influence effective financial tasking.

In the present study, financial literacy was considered as belonging to the capacity dimension, decisions about FPR are within disposition dimension, financial management belongs to the opportunity dimension and parental economic socialization is a distal antecedent of FPR because, as pointed out by some authors, financial lessons learned in childhood could have an impact 20 or 40 years later (Dan, 2004). Therefore, the main goal of this work is to determine the extent to which parental economic socialization accounts for individuals' FPR by means of various mediator processes.

FINANCIAL PLANNING FOR RETIREMENT (FPR)

Savings have been and continue to be the main starting point to describe financial behavior and, normally, people accumulate their savings during their professional careers to have economic resources during retirement. Many recent studies have focused on FPR (among others, Love et al., 2008; Venti, 2011) because planning the financial aspect of retirement is increasingly important to ensure one's financial security at this stage (McLaughlin, 2016; Whitley et al., 2016).

This planning consists of assessing future financial needs and saving to achieve economic well-being during retirement. Considering the studies that have investigated FPR, it has been observed that planning and saving for retirement is related to a feeling of financial security and to the acquisition of more wealth in comparison with those who do not plan economically (Ameriks et al., 2003; Ekici and Koydemir, 2016). In addition, the perception of social norms could affect the tendency to plan and save, as well as the impact of the person's financial knowledge and skills (Hershey et al., 2013). Financial literacy has received the most attention concerning FPR and it has been related to saving for retirement (Hershey et al., 2007; Gutierrez and Hershey, 2013; Kiso and Hershey, 2016; Koposko et al., 2016).

PARENTAL ECONOMIC SOCIALIZATION

During adolescence and later on during youth, individuals try out familiar behaviors and new behaviors in order to learn how to be adults (Campbell, 1969; Montoya-Castilla et al., 2016). In the economic context, this translates into a progressive attempt to individually resolve economic problems that arise in daily life. Economic psychology considers both the influence of economy and of the social and cultural environment; in the case of children and adolescents, their parents are the main environmental influence (Sonuga-Barke and Webley, 1993). In addition, adolescence is an important life stage in which economic socialization occurs, as specific attitudes toward saving develop. Recent research indicates that early experiences continue to be associated with attitudes, even in later life, and may not be completely overridden by adult experiences (Ward, 2013).

Previous studies showed that parental economic behavior had an impact on the children's economic behavior (Feather, 1991). Subsequently, Otto (2009) studied parents' role in the development of their children's saving skills during adolescence, finding that their saving example influenced their children's saving skills. In the same line, other works have found that parental economic socialization is related to children's greater financial literacy in adolescence (Gutierrez and Hershey, 2014) and it also predicts saving behavior (Hira et al., 2009). Similar results were also found in older samples, which showed that parental economic socialization also influenced university students' saving behaviors and economic planning (Thung et al., 2012).

To sum up, early influences had a large impact on saving behavior in later life, as Brown and Taylor (2016) stated. In this sense, it should not be forgotten that, as a result of the economic crisis that originated in 2008, people are more interested in improving their financial skills and are gradually taking on more personal responsibility to achieve financial well-being. On the basis of this literature, the present work proposes that:

- H1: Parental economic socialization will predict FPR.

FINANCIAL LITERACY

As stated in above, it seems reasonable to think that the relation between parental economic socialization and FPR is indirect and may be influenced by other not yet clearly established variables, partly because the transition from childhood to adulthood is understudied by economic psychology (Otto, 2009). Accordingly, one of the possible mediators is financial literacy. This consists of the skill to read, manage and analyze the personal finances that have an impact on one's financial well-being (Nawaz, 2015). We know that receiving financial education can improve both financial behavior and literacy since empirical results in this regard have been found.

First, it was noted that taking finance courses improved the financial behavior of adults aged between and 25–55 years (Lyons et al., 2006). Second, with regard to FPR, various works have found that financial literacy is positively related to saving behavior, to investment performance (Nawaz, 2015), and to pension plan participation (Koposko et al., 2016). In addition, it was found that people with more financial literacy plan for their retirement to a greater extent (Koposko and Hershey, 2014). Finally, Drever et al. (2015) have recently proposed a theoretical model that relates economic socialization to responsible and efficient financial management through the development of literacy, specific cognitive skills, and personality characteristics that promote financial management in adulthood. Hence, the present study proposes:

- H2: The relation between parental economic socialization and FPR will be mediated by financial literacy.

DECISIONS ABOUT FPR

The decision to prepare for retirement constitutes the prior stage to preparation for retirement *per se*, and specifically, economic preparation is one of the most important aspects to be planned. The decision to start preparing for retirement largely depends on socially accepted norms (Goodnow, 1997). Thus, people often begin to prepare for retirement when they notice that their coworkers or peers begin to prepare for it. In addition, various studies were conducted to discover the factors that influence the decision to prepare economically for retirement. First, it has been observed that the decision is influenced by the person's vision of the future, such that people who live from day to day will find it difficult to decide to plan financially for retirement (Jacobs-Lawson and Hershey, 2005). In addition, having sufficient economic resources to save has also been associated with the decision to prepare financially for retirement (Hira et al., 2009). Furthermore, this decision also depends on people's retirement goals, for example, if they intend to travel a lot at this stage, they are more likely to decide to plan and save for retirement (Schulz, 2002). To sum up, the lifespan planning and decision making would be influenced by personal experiences (Smeaton et al., 2017), as early financial learning (Koposko and Hershey, 2014). Therefore, in the present work, we propose that parental economic socialization will exert indirect influence on FPR through decisions about FPR.

- H3: The relation between parental economic socialization and FPR will be mediated by the decisions about FPR.

FINANCIAL MANAGEMENT

Initially, Deacon and Firebaugh (1988) stated that financial management includes a series of behaviors aimed at planning, implementation, and assessment in the areas of cash, credit, investments, insurance and retirement. With regard to consequences of financial management, it has been observed that, when families use effective financial management, their economic welfare improves, whereas inadequate financial management can lead to negative social consequences at the long term (Choi, 2017). If the income of a family is inadequate to meet the financial obligations, the capacity to save will be affected (Garasky et al., 2008). It has also been observed that youth practice fewer basic financial skills, such as budgets, developing regular savings plans or planning for long-term needs (Birari and Patil, 2014).

Financial management involves a series of behaviors that differ in their frequency among individuals, for example, paying with credit cards tends to be more common than signing a pension plan. It has also been pointed out that repeated exposure to and practice of financial activities could help to develop financial literacy and skills in economic transactions (Jorgensen and Savla, 2010). Lastly, it was found that people who score high in financial management have higher levels of savings and lower levels of debt (Dew and Xiao, 2011). To sum up, as life course perspective stated (Elder, 1998); individuals are influenced by significant others and, at the same time, they could shape their lives by choosing certain activities to engage. Hence, parental economic influences could be combined with personal decision to plan and save. This may have important implications in FPR because, as noted, parental economic socialization has an impact on present and future economic behavior and general financial management is one of these behaviors.

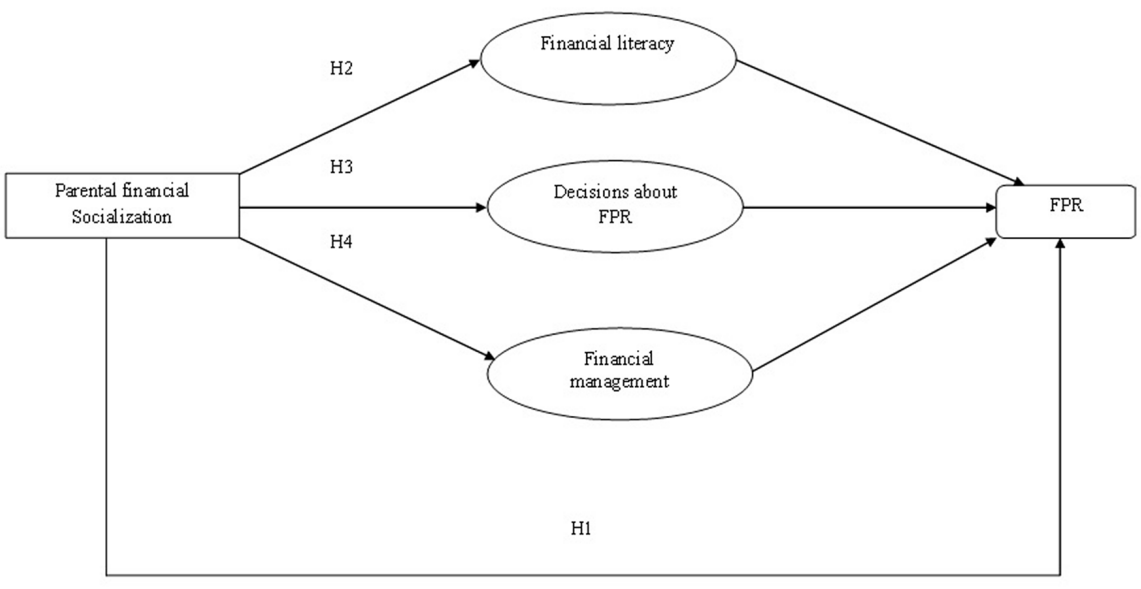

FIGURE 1 | Hypothesized model for the study. Note: FPR, financial planning for retirement.

- H4: The relation between parental economic socialization and FPR will be mediated by financial management.

The hypothesized model for this study is displayed in **Figure 1**.

MATERIALS AND METHODS

Participants

Following the "two-stage sampling" approach suggested by Van Solinge (2013), a specific pool of small and medium-sized enterprises was selected first, and the actual population of workers aged between 45 years and 63 years in the firms concerned were then invited to participate. This procedure allows us to avoid some shortcomings of the empirical studies on retirement. On the one hand, empirical studies are often criticized for relying on convenience samples affected by unknown selectivity issues. On the other hand, certain published studies take representative national samples so as to obtain generalizable results for the population of older adults as a whole. However, this involves further restrictions in order to whittle samples down to the limited number of participants actually transitioning to retirement.

Hence, our procedure entailed two steps. The research group contacted 10 firms to propose a broad study of human resources management. The eight firms that responded were then visited by the researchers to explain the criteria for the inclusion of participants (current employees over the age of 45 years). Only five organizations finally took part in the study. During May–July of 2017, 355 current employees aged 45 years or older received the questionnaire, a letter explaining the purpose of the study and the data collection procedure, and an envelope to return the survey directly to the Research group. Those employees who agreed to participate completed the questionnaires individually and outside of their workplaces. We eventually collected 302 completed questionnaires, yielding a response rate of 85%. Questionnaires missing more than 25% of the data were excluded, yielding a final sample of 280 Spanish participants.

The Ethical Committee of the three authors' University Bio-ethical Committee of the National Distance Education University (UNED) approved the Project at May 2016. This study was carried out in accordance with the recommendations of Declaration of Helsinki revised in Fortaleza (World Medical Association [WMA], 2013), followed and approved by the Bio-ethical Committee of the National Distance Education University (UNED). All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Bio-ethical Committee of the National Distance Education University (UNED). Confidentiality was maintaining by data being de-identified prior to data analysis by the deletion of identifiable material. Regarding gender, 59.3% of the sample was female (40.7% male). The participants' mean age was 53.08 years (SD = 5.06). The most predominant professional categories were employee (62.5%) and intermediate manager (22.5%). Mean job tenure in the company was 19 years (SD = 10). Concerning education, 40.7% of the sample had university studies, and 30.7% up to high school. Moreover, 29.3% worked in the health setting, and 22.5% in the technological setting. Regarding job status, 89.3% worked full time, and 2.9% were part-time employed. With regard to retirement, 55% thought they could retire at age 65 years and 17% at 67 years.

Measures

Demographic data, including the age, gender, level of training and education, number of dependants in the household, work setting, job tenure in the company, employment status, professional category and estimated retirement age were collected from the participants through a set of items included at the beginning of the questionnaire. Regarding the structure of the questionnaire, all the items of the following scales were mixed in a random order.

Parental Economic Socialization

We used a scale adapted to adults with eight items to measure parental economic socialization based on the "Parents as a guide" subscale included in the "Saving Attitude Scale" of Otto (2009) and the "Parental Socialization Scale" of Thung et al. (2012). Example items of this scale are: "I usually save because my parents taught me to do so when I was a child" or "My parents are proud of me because I am thrifty". All the items were rated on a five-point response format ranging from 1 (strongly disagree) to 5 (strongly agree). This measure has shown high internal consistency in the past (α = 0.75; Thung et al., 2012) and the value of Cronbach's alpha found in this study was 0.86.

Financial Literacy

We used a six-item scale to measure individuals' general financial literacy (Hershey and Mowen, 2000; Jacobs-Lawson and Hershey, 2005). Example items of this scale are: "I know a lot about FPR" or "When I need to consult about finances I know exactly where to get the information". All items are rated on a 5-point response format ranging from 1 (strongly disagree) to 5 (strongly agree). This measure has shown high levels of internal consistency in the past (α = 0.94; Jacobs-Lawson and Hershey, 2005) and the value of Cronbach's alpha found in this study was 0.77.

Decisions About FPR

The decisions about FPR were measured by means of the Financial Preparation subscale included in the "Decision to Prepare for Retirement Scale" (Noone et al., 2010). The participants completed four items using a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Examples of these items are: "In my financial situation, I think it's too early to begin to think about when I retire" or "I shall worry about financial issues when I am closer to retirement". This measure has shown high internal consistency in this study (α = 0.73).

Financial Management

We used the Financial Management Scale (Dew and Xiao, 2011), which consists of 15 items included in four subscales (savings and investments, cash management, credit, and insurance management). The instructions were: "Please

TABLE 1 | Descriptive statistics and correlation matrix of variables (N = 280).

Variables	M	SD	1	2	3	4	5	6	7
Control variables									
1. Age	53.08	5.06	–						
2. Number of dependants	1.04	1.16	−0.34**	–					
3. Organizational tenure	18.81	10.01	0.40**	−0.08	–				
Predictor variables									
4. Parental economic socialization	3.33	0.78	−0.02	0.12*	0.06	–			
5. Financial literacy	2.84	0.73	−0.13*	0.19*	−0.05	0.27**	–		
6. Decisions on FPR	3.26	0.81	0.18**	−0.01	0.02	0.12*	0.31**	–	
7. Financial management	3.23	0.55	−0.10	0.08	−0.02	0.33**	0.44**	0.30**	–
Criterion variable									
8. FPR	2.76	0.84	0.15*	−0.01	0.15*	0.14*	0.25**	0.19**	0.41**

*Note: *p < 0.05; **p < 0.01.*

indicate the frequency with which you have carried out the following activities in the past 6 months". Examples of the items used are: "Paying all your bills on time" or "Buying bonds, shares, or funds". All items used a 5-point response scale ranging from 1 (never) to 5 (always). This measure has shown high values of internal consistency in the past (α = 0.81; Dew and Xiao, 2011), and the value of the Cronbach's alpha found in this study was 0.73.

FPR

To measure FPR, we used the Financial Planning for Retirement Scale (Stawski et al., 2007). Participants completed nine items using a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). The instructions required participants to answer items about the financial planning activities they had carried out in the past 12 months. Example items are: "I have made specific expenditure plans for the future" and "I have made voluntary contributions to a savings plan for retirement." This measure has shown high values of internal consistency in the past (α = 0.87; Stawski et al., 2007), and the value of Cronbach's alpha found in this study was 0.74.

RESULTS

Descriptive Analyses and Correlations

The means, standard deviations and correlations of all the variables in this study are shown in **Table 1**. Related to control variables, both age and organizational tenure also correlated positively and significantly with FPR (both r = 0.15, $p < 0.05$), but the number of dependants and estimated age of retirement correlated negatively but non significantly with FPR. FPR was significantly and positively correlated with parental economic socialization (r = 0.14, $p < 0.05$), financial literacy (r = 0.25, $p < 0.01$), decisions about FPR (r = 0.19, $p < 0.01$), and financial management (r = 0.41, $p < 0.01$).

With regard to the descriptive statistics of the target variables, the highest score was observed in parental economic socialization (M = 3.33, SD = 0.78), the lowest score in financial literacy (M = 2.84, SD = 0.73), and FPR obtained a mean of 2.76 (SD = 0.84).

Hypothesis Testing

We analyzed the relation of parental economic socialization with FPR, both directly and considering the variables financial literacy, decisions about FPR and financial management as mediators. To test the first hypothesis of the study, linear regression analysis was conducted, entering the control variables in the first step (Model 1: age, number of dependants in the household and job tenure in the company), and parental economic socialization was entered in the second step (Model 2). The first step was nonsignificant, but in the second step, parental economic socialization predicted FPR positively and significantly (β = 0.14, $p < 0.05$), which provides support for Hypothesis 1. However, the values of R^2 were not higher than 0.10.

To analyze the mediation hypotheses, we used the INDIRECT macro for SPSS elaborated by Preacher and Hayes (2008). The direct effect of parental economic socialization on FPR was nonsignificant in all of the three mediation cases: financial literacy (c' = 0.08, p = 0.24), decisions about FPR (c' = 0.12, p = 0.05), and financial management (c' = −0.01, p = 0.92). Likewise, with a 95% confidence level, the confidence intervals (CI) did not include the value 0 (CI financial literacy [0.03, 0.13], decisions about FPR [0.002, 0.07] and financial management [0.10, 0.24]), so the indirect effect was significant. Therefore, the results confirmed that financial literacy, decisions about FPR and financial management mediated the relation between parental economic socialization and FPR, which confirms Hypotheses 2–4 (**Tables 2**–**5**).

TABLE 2 | Linear regression analysis on FPR.

Predictor variables	FPR	
	Model 1 β[a]	Model 2 β[a]
Age	0.12	0.12
Number of dependants	0.04	0.02
Organizational tenure	0.11	0.10
Parental economic socialization		0.14*
R^2	0.03	0.05
F	2.45*	3.09*
ΔR^2	0.03	0.02
ΔF	2.45*	5.46*

*Note: [a]Standardized regression coefficients; FPR, Financial Planning for Retirement (N = 280). *p < 0.05.*

TABLE 3 | Regression results for testing mediation of financial literacy in the relationships between parental economic socialization and FPR.

	Coeficient	SE	*t*	axb	EE	95% CI
Total effect	0.15*	0.06	2.34			
Direct effect	0.07	0.07	1.16			
H2: Parental economic socialization → Financial literacy → FPR				0.07	0.02	[0.03, 0.13]

*Note: N = 280; SE, Standard error; CI, confidence interval; unstandardized regression coefficients are reported. Bootstrap sample size = 10.000; *p < 0.05.*

TABLE 4 | Regression results for testing mediation of decisions on FPR in the relationships between parental economic socialization and FPR.

	Coeficient	SE	*t*	axb	EE	95% CI
Total effect	0.15*	0.06	2.34			
Direct effect	0.12	0.06	1.97			
H3: Parental economic socialization → Decisions on FPR → FPR				0.02	0.01	[0.002, 0.07]

*Note: N = 280; SE, Standard error; CI, confidence interval; unstandardized regression coefficients are reported. Bootstrap sample size = 10.000; *p < 0.05.*

TABLE 5 | Regression results for testing mediation of financial management in the relationships between parental economic socialization and FPR.

	Coeficient	SE	*t*	axb	EE	95% CI
Total effect	0.15*	0.06	2.34			
Direct effect	−0.01	0.06	−0.10			
H4: Parental economic socialization → Financial management → FPR				0.16	0.03	[0.10, 0.24]

*Note: N = 280; SE, Standard error; CI, confidence interval; unstandardized regression coefficients are reported. Bootstrap sample size = 10.000; *p < 0.05.*

DISCUSSION

In the environment of accelerated economic changes currently undergone by society, people must increase their responsibility for their economic stability in the last stages of their lives. For this purpose, they should improve their decisions and financial skills because these will allow them to perform more responsible financial behavior. The role of the parents as socializing agents is very important for the origin and development of these decisions and skills. In addition, we know that parental financial teaching influences the efficacy of financial behaviors (Shim et al., 2015).

The main goal of this work was to determine whether parental economic socialization was positively related to FPR through other variables, thus providing support for the hypotheses proposed from the model of Hershey et al. (2013). First, parental economic socialization was positively and significantly related to FPR through financial literacy, coinciding with the findings of other recent studies (Shim et al., 2015). Moreover, our study empirically verifies some of the theoretical formulations presented by Drever et al. (2015), who establish a model of relations between economic socialization and responsible financial management through a set of mediator variables such as skills, literacy and personality traits.

Second, it is interesting that some works did not find a relationship between financial literacy and FPR or else they found a very weak one (Tang et al., 2015). Likewise, in another work, no differences were observed between the financial behavior of people who took a financial course and that of those who did not (Mandell and Klein, 2009). In any case, there seems to be empirical evidence that parental socialization plays a role in facilitating and promoting saving behavior, even a long time later. Accordingly, our findings agree with other works that indicate strong links between parental influence and responsible financial behavior, confirming these relations in longitudinal investigations with more than 20 years of follow-up of the participants, such as study of Tang et al. (2015) or, with a shorter interval, in the work of Shim et al. (2015), or Trzcińska and Goszczyńska (2015).

Third, parental economic socialization is positively and significantly related to FPR through decisions about FPR (H3). This coincides with the idea that what we learn from our parents and what they teach us about economic issues and savings has an impact on the decision to plan the financial aspect of retirement, and this decision is the first step of planning for retirement. Thus, Koposko and Hershey (2014) find that early parental influences affect future time perspective and retirement goal clarity, which are the antecedents of the tendency to plan and save. On another hand, it has been noted that this decision could also be affected by the person's estimation about his or her future retirement needs and, despite the importance of these decisions, it is remarkable that there are so few empirical works on the topic (Topa et al., submitted). In any event, very promising pathways of future research are opening because parental socialization practices could also be influencing through the perceptions of financial self-efficacy that children develop, which have been shown to be predictors of positive retirement outcomes in other studies (Montford and Goldsmith, 2016).

Fourth, it should not be forgotten that various works indicate that the family is not the only influence in financial decisions, but instead they are also influenced by comparisons with peers (Koposko et al., 2016), or by socialization coming from other sources. Accordingly, particularly important is the work of Dávila et al. (2016), which compares peer influence and parental influence in Spanish children, concluding that the former have

more impact than the latter on classmates' materialism. These results should be related to our findings on the family in future research. In the same vein, also extending the period of familiy influences taken into account could be useful, along with developing other approaches as generational to expand future findings (Lim et al., 2015).

Fifth, parental economic socialization was positively and significantly related to FPR through financial management, supporting the last hypothesis of this investigation (H4). In a similar vein, it has been observed that financial management is related to people's financial attitudes (Mien and Thao, 2015), and economic socialization plays an important role in these attitudes. Although the socialization of parents on FPR is fundamental, as the study underlines and concludes, in a context of unemployment and job insecurity and a consumer society such as the current one, it is interesting to not forget that working conditions in adulthood, political and social disaffection that could also influence financial decisions, as an anonymous reviewer suggested.

With regard to the theoretical implications of the present investigation, to our knowledge, there are no precedents that have examined parental socialization from the perspective of a full model of FPR, although there are works about responsible financial behavior in general (Shim et al., 2015; Tang et al., 2015), or retirement attitudes (Macewen et al., 1995). Despite the fact that empirical studies on FPR have been conducted from other theoretical perspectives, such as the theory of planned behavior (Thung et al., 2012), the model used herein takes into account various dimensions that affect FPR, and allows developing more solid hypotheses. Thus, taking the data as a whole, empirical support was obtained for the indirect relation between parental economic socialization and FPR.

Limitations

As this is a cross-sectional study, we did not analyze the changes that occur in the variables as time elapses, and this must be taken into account when interpreting the findings of this research because longitudinal works are often found in economic psychology (Shim et al., 2015; Tang et al., 2015). In any event, these works frequently focus on the general population of children or adolescents, and not on the study of adults' FPR with these designs. Despite the cross-sectional nature of the data, we highlight that most investigations on this topic use the same type of design, due to the difficulty of collecting data about parental socialization in childhood and adolescence in order to assess its influence on adults' FPR 40 years later.

In addition, the representativeness of the Spanish sample used hinders generalization of the results, as we know that depending on the culture and the pension systems (Khan et al., 2016); some variables may be more significant than others in predicting FPR (Mansor et al., 2015). Notwithstanding, diverse studies of parental economic socialization carried out with very diverse samples such as Europe (Otto, 2009), the United States (Koposko and Hershey, 2014), Poland (Trzcińska and Goszczyńska, 2015) or Malasia (Thung et al., 2012) have shown consistent relations between parental influences and saving behaviors. On another hand, there are various measures of financial management, and some of them focus more on saving management, investment management, or cash management. Here, we chose a global measure, and this may affect the results (Resende and Zeidan, 2015). With regard to the procedure used to collect the data, self-report measures may lead to common variance error. In this sense, some recent works indicate the need for standardized measurement instruments to assess financial literacy, as the different measures can lead to results that may not be comparable (Schmeiser and Seligman, 2013). In relation to these methodological issues, some authors also point out that the position of key information in documents and advertisements concerning financial products can affect the accessibility of the information and, as a result, influence decision-making (Foster et al., 2015).

Future Lines of Research

This work coincides with other studies in which the model of behavior that the parents teach their children has a positive impact on the development of financial behaviors and literacy but it would be interesting to explore whether parental economic socialization has negative repercussions on the children's economic decisions and behaviors. Nevertheless, future works could examine the weight of different types of economic socialization (parents, teachers, peers, etc.) on FPR because, although parents are the first source of influence, other models of financial behavior may influence throughout adolescence and adulthood, and it would be appropriate to study the interaction between all of them, as outlined above.

In the same vein, future research would consider that parental economic socialization should interact with emotions or other individual features (Rodríguez et al., 2015; Yu and Chen, 2016) or personality characteristics (Topa and Herrador-Alcaide, 2016) in order to affect retirement planning.

Moreover, despite the fact that our participants were 60% women, it seems that there is no influence of gender from the professional profile of respondents. Due to the fact that the influence of being female would be greater according to the differences on socio-economic status, as professional levels and salary, future research should take into account a different other profiles of lower professional women, along as different sectors or work (Haratsis et al., 2015).

In the socialization of parents it would be interesting to provide a gender perspective and to analyze, for future studies, whether the father's influence is greater in that he usually has better working conditions (higher wages to equal work than women) and is usually the "bread winner or head of household" and decide more on family economic issues. Or, on the contrary, it is already mothers (with their double role as housewives and paid workers) who are increasingly influencing this. Due to gender differences, perhaps mothers tend to be less charged and therefore less influential on these issues, as an anonymous reviewer suggested.

Additionally, for future research, a qualitative sample could be used based on some in-depth interviews or discussion groups

for children/youth or adults. These techniques would allow us to obtain opinions on the values, attitudes and expectations (desires or reality) of these groups of people on important subjects that are discussed here: savings/spending, consumption and consumerism, need for preparation and training for retirement economic security) from childhood to improve intergenerational relations, need for savings for reasons of leisure, health, future care, etc. Especially due to the fact that the family or the State can no longer cover this service anymore (Van der Heijden et al., 2016).

In addition, the role of the level of income in the relationship between financial literacy and FPR should be of examined because authors like Pahnke and Honekamp (2010) found that financial literacy was positively related to FPR only in the case of high economic income. Lastly, we wonder whether parents' teachings about economic material are direct—through their communication—, indirect—by means of observation—, or whether both of them interact and if so, how, in order to establish the most efficacious parental socialization practices in this matter, as proposed from developmental psychology (Shim et al., 2015).

Practical Implications

This work reveals the importance of parental economic teachings, both at the level of theoretical and practical knowledge, in the individuals' saving decisions for FPR. In a similar vein, continuing with the development of financial education, schools should include classes or courses to improve financial skills and knowledge that enable students to interpret the information they receive from television, internet, banks, etc.

Likewise, for the adult population, programs of credit counseling could be created that highlight the benefits of long-term saving for financial security. Thus, instruction in economics and saving would be more complete and continued lifelong, as it is important to properly deal with possible economic changes that may arise at the family level (e.g., occupational dismissal, retirement) or at the population level (e.g., economic crisis, changes in the system of pensions; Han et al., 2015). As recent empirical research stated, the relationship between financial hardship and impaired well-being is strong (Annink et al., 2016). Moreover, counseling interventions should be expanded, in order to include novel findings regarding the use contemplation in the context of financial management. As an experimental study showed (Harkin, 2017), promting participants to contemplate their debt and expenditures would improve financial decision-making, by reducing the likelihood of avoid debt-related information and improve estimates of expenditures.

To sum up, this work supports earlier studies that show that parental financial behavior impacts on children's FPR, and it is a positive model for the development of financial literacy and skills and for decisions about FPR. Thereby, the findings support the idea that FPR can and must start at youth because we have the tools for this purpose, and delaying FPR could reduce the likelihood of success. Hence, this initial learning, complemented with others developed during adulthood, is of great relevance for FPR.

AUTHOR CONTRIBUTIONS

FP, IJ and GT made substantial contributions to the conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Depression and Dementia in Old-Old Population: History of Depression May Be Associated with Dementia Onset. The Tome Project

Yi-Chien Liu[1,2,3], Kenichi Meguro[1], Kei Nakamura[1], Kyoko Akanuma[1], Masahiro Nakatsuka[1], Takashi Seki[1], Shutaro Nakaaki[4], Masaru Mimura[4] and Norito Kawakami[5]*

[1] Division of Geriatric Behavioral Neurology, Cyclotron and Radioisotope Center (CYRIC), Tohoku University, Sendai, Japan, [2] Neurological Center of Cardinal Tien Hospital, Taipei, Taiwan, [3] Fu Jen University School of Medicine, Taipei, Taiwan, [4] Department of Neuropsychiatry, Keio University, Tokyo, Japan, [5] School of Public Health, University of Tokyo, Tokyo, Japan

Background: In this study, we investigated the relationship among a history of depression, depressive states, and dementia in a community-based old-old cohort.

Methods: From 2012 to 2013, we recruited 200 subjects residing in Tome, Japan. Ultimately, 181 subjects were enrolled in our study and completed the whole study protocol. We used the World Mental Health-Composite International Diagnostic Interview 3.0 to evaluate whether subjects had a history of depression or other affective disorders. Simultaneously, 3.0 Tesla brain magnetic resonance imaging (MRI) was performed for each subject.

Results: Of 181 subjects, 66 were normal (clinical dementia rating [CDR] = 0), 88 had MCI (CDR = 0.5), and 27 had dementia (CDR = 1 or above). Nine of the 181 subjects (4.9%) had a history of depressive episodes. CDR was significantly higher in subjects with a history of depression (0.9 vs. 0.4, $p = 0.046$) than in those without it. Seventy-two of the 181 subjects (39.7%) exhibited depressive symptoms. Subjects with depression exhibited lower Mini–Mental State Examination scores (21.6 vs. 23.3, $p = 0.008$), higher CDR scores (0.6 vs. 0.3, $p = 0.004$), and more atrophy of the medial temporal lobe (4.4 vs. 3.7, $p = 0.036$).

Conclusion: A history of depression should be considered a risk factor for all-cause dementia. In the old-old population, depression is associated with a higher prevalence of dementia, lower cognitive performance, and a smaller hippocampus.

Keywords: senile depression, history of depression, dementia, CIDI, MRI

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***Correspondence:**
Kenichi Meguro
k-meg@umin.ac.jp

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INTRODUCTION

Depression and dementia are very common mental disorders in the elderly population. However, their relationship is not yet fully understood. A systemic review of Alzheimer disease found that a history of depression is an important risk factor (Ownby et al., 2006). Other studies have also demonstrated a strong relationship between late-life depression and all-cause dementia (Gatz et al., 2005; Li et al., 2011; Diniz et al., 2013). Although depression is a common symptom in early stage of Alzheimer's disease (Spalletta et al., 2010), whether depressive symptom persisted or recovered during follow up is also an important predictor of further cognitive deterioration

(Spalletta et al., 2012). However, inconsistent findings have been obtained for the relationship between depression and dementia. Several community-based longitudinal studies have not found a connection between depression and dementia development (Becker et al., 2009; Luppa et al., 2013). One twin-based study even found depression to be a prodrome of dementia, but early-life depression was not identified as a risk factor (Brommelhoff et al., 2009).

Several hypotheses have been proposed to explain the possible connection between depression and dementia. The most well-known and consistent hypothesis is the presence of white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) (Herrmann et al., 2007). WMHs may disrupt the connecting fibers between cortical and subcortical areas in the brain. Most studies have found that WMHs possibly contribute to the pathogenesis of both late-life depression and Alzheimer disease (O'Brien et al., 1996; Taylor et al., 2003). Deep white matter lesions may also be more related to late-life depression. By contrast, periventricular lesions may be more related to Alzheimer disease (Krishnan et al., 2006). In addition to their relationship with depression, WMHs may even impair attention and executive functions in subjects without dementia (Ishikawa et al., 2012). Some studies have demonstrated that subjects with WMHs exhibit poor prognosis and poor responses to medication (Godin et al., 2008).

Another possible structural change related to both depression and dementia is a smaller hippocampus, which has been documented in many epidemiological studies (Campbell et al., 2004; Videbech and Ravnkilde, 2004). Reduced hippocampal volume has also been observed in subjects with post-traumatic stress disorder and other psychiatric disorders (Geuze et al., 2004). The chronic effects of stress hormones, including glucocorticoid and catecholamine, have been most frequently implicated as the causative factor of this structural change (Lupien et al., 2007).

In this study, we focused on the old-old population (age more than 75 years) in a community-based sample. In the old-old population, depression is a serious health problem and is related to poor nutrition, a higher institutionalization rate, and a higher mortality rate (Van Leeuwen Williams et al., 2009). However, few studies have focused on depression in this population. In this study, we investigated the relationship among a history of depression, depressive symptoms, and dementia in this population. Especially, we focused on lifetime history of depressive episodes and their relationship between cognitive function. For detailed records of lifetime depressive episodes, we used WMH-CIDI (World Mental Health-Composite International Diagnostic Interview) for diagnostic interview. We also examined any possible white matter changes and hippocampal atrophy in brain MRI by using different visual rating scales.

MATERIALS AND METHODS

Participants

This community-based study of depression and dementia, the Tome Project, was conducted in Tome, Miyagi Prefecture, Northern Japan. From 2012 to 2013, we randomly selected 200 residents aged more than 75 years, of whom 181 agreed to participate in our project and completed the study protocol. The study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Neuropsychological Tests

Mini–Mental State Examination

In this study, the Japanese version of the Mini–Mental State Examination (MMSE) (Ideno et al., 2012) was used to evaluate general objective cognitive function.

Clinical Dementia Rating

The clinical dementia rating (CDR) of each participant was determined by the clinical team, comprising medical doctors and public health nurses, who were blinded to the cognitive test results. Before participants were interviewed by the doctors, the public health nurses visited the participants' homes to evaluate their daily activities. The public health nurses completed a semi-structured questionnaire by using the families' observations of the participants' lives. Participants who lived alone were excluded from this investigation. Participants were then interviewed by the doctors to assess their episodic memory, orientation, and other variables. Finally, based on the information provided by the families, the participants' CDR stages were determined at a joint meeting. A reliable Japanese version of the CDR worksheet (Meguro, 2004) was established, and dementia was diagnosed based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, Edition IV (DSM-IV). One author (K.M.) was certified as a CDR rater at the Washington University School of Medicine Alzheimer's Disease Research Center Memory and Aging Project. We used CDR to evaluate the impairment in daily life caused by cognitive disturbance. The evaluation of CDR was based on five levels (0, 0.5, 1, 2, and 3) in six domains (memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care).

World Mental Health-Composite International Diagnostic Interview

The World Mental Health-Composite International Diagnostic Interview 3.0 (WMH-CIDI 3.0) is a fully validated, structured diagnostic tool (Kessler and Ustün, 2004). In this study, trained interviewers (a clinical psychiatrist and one of the authors, K.N.) clinically diagnosed recent and lifetime mental disorders by using the Japanese version of the CIDI. A previous study demonstrated good concordance between the clinical diagnosis and the diagnosis obtained using the Japanese version of the WMH-CIDI (Sakai et al., 2003). Diagnostic interviews were conducted to record depressive episodes, including lifetime major depressive disorder (MDD), lifetime major depressive episodes (MDEs), 12-month MDEs, 30-day MDEs, and 30-day MDD with hierarchy.

Geriatric Depression Scale

In this study, we used the Japanese version of the 15-item geriatric depression scale (GDS) to evaluate depressive symptoms in our subjects. This version of the GDS has been validated in the Japanese population (Sakai et al., 2003). All items in the GDS are rated by self-report as 0 or 1, where 0 = yes and 1 = no. Finally, the total score is calculated, with higher scores indicating more severe depression. Depression was defined as scores higher than the cutoff points (4/5). Subjects with scores of 5 or more were considered depressive, and those with scores of 4 or less were considered nondepressive.

Brain MRI Acquisition

All participants received whole-brain MRI scans (Vantage Titan 3T, Toshiba, Tokyo, Japan) in the clinical assessment. 2D axial fluid-attenuated inversion recovery (FLAIR) images (TR/TE = 10,000/108 ms, Inversion time = 2,700 ms, NEX = 1, Voxel size = $0.3125 \times 0.3125 \times 5\,mm^3$), and high-resolution sagittal T1-weighted images (TR/TE = 13.5/5.5 ms, NEX = 1, Voxel size = $0.3618 \times 0.3618 \times 1\,mm^3$) were acquired. The image analysis included a visual rating of WMH on FLAIR and MTA on theT1-weighted images.

Evaluation of Medial Temporal Lobe Atrophy

We evaluated medial temporal lobe atrophy (MTA) in the coronal plane through T1-weighted images. MTA was rated on a 5-point scale (0, absent; 1, minimal; 2, mild; 3, moderate; and 4, severe) based on the height of the hippocampal formation and the width of the choroid fissure and the temporal horn (Kim et al., 2014; **Figure 1**). The MTA scale was applied to the right and left medial temporal lobe. In our analysis, the dichotomized score of left and right was used.

Evaluation of White Matter Hyperintensities, Periventricular Hyperintensities, and Deep White Matter Hyperintensities

Lesions adjacent to the lateral ventricles on T2-weighted images were evaluated. The anterior and posterior parts of the periventricular hyperintensities (PVHs) were scored on a 4-point scale (0: absent, 1: minimal, 2: mild, punctuate but thin, 3: definite, and 4: confluent). Finally, the scores of both parts were summed up to yield the total score for PVH. Similarly, deep white matter hyperintensities (DWMHs) were also evaluated on a 4-point scale (0: absent, 1: numbers were less than 5 or the maximum size was <4 mm, 2: numbers were more than 5 and less than 10 or the maximum size was 4–8 mm, 3: numbers were more than 10 and maximum size was >8 mm, and 4: confluent). The scores of bilateral DWMH were finally summed up to yield the total score for DWMH (Ishii et al., 2006).

Evaluation of Cholinergic Pathways Hyperintensities Scale Scores

Using FLAIR images, we evaluated WMH lesions involving the cholinergic pathways. The visual rating of the cholinergic pathways hyperintensities scale (CHIPS) required four representative axial images. These four index images included the medial (cingulate gyrus) and lateral (external capsule, claustrum) cholinergic pathways. Using landmarks of the third ventricle, lateral ventricle, and corpus callosum, we analyzed 10 regions using a 3-point scale (0: normal, 1: mild, and 2: moderate to severe) (**Figure 2**). Each slice was weighed to account for the decreasing concentration of cholinergic fibers. Finally, the total CHIPS score ranged from 0 to 100 (Bocti et al., 2005).

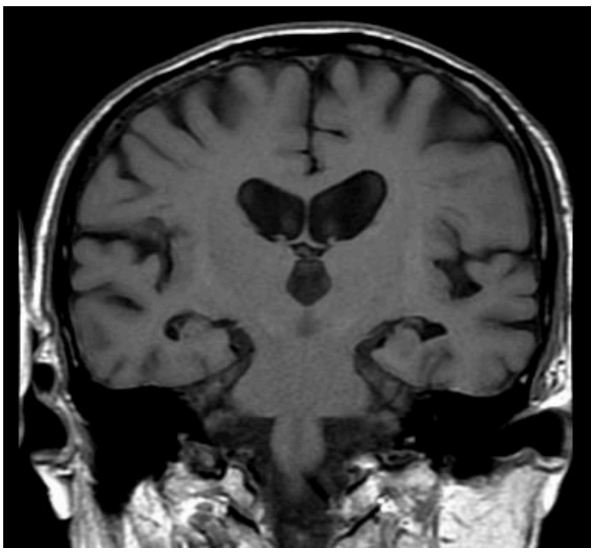

FIGURE 1 | Medial temporal atrophy (MTA) scoring illustrated on T1-weighted MRI. The degree of MTA was rated on a 5-point scale from absent (0) to severe (4). The MTA score of this patient is 2 (right: 2, left: 2).

Statistical Analyses

All analyses were performed using the Statistical Package for the Social Sciences, Version 22 (SPSS, Chicago, IL, USA). Demographic variables were compared using one-way analysis of variance, Student's *t*-test, and the Chi-square test, as appropriate. Besides analysis of total participants, we also performed multiple comparison analysis between three groups (CDR 0, 1, and 1+). Because of the relatively small number of subjects with a history of depression, we used nonparametric statistics (Mann–Whitney U test) and Fisher's exact test for such comparisons.

RESULTS

Demographic Data

Of 181 subjects, 66 were normal (CDR = 0), 88 had MCI (CDR = 0.5), and 27 had dementia (CDR = 1 or above) (**Table 1**). Nine of the 181 subjects (4.9%) had a history of depressive episodes. In the three groups (dementia, MCI, and normal), 51.9, 60.2, and 53.0% were women, respectively. Comparison of the three groups showed no significant difference ($p = 0.59$). Age was significantly higher in the dementia group (84.0 vs. 80.9 vs. 79.2, $p < 0.001$). Years of education were lower in the MCI and dementia groups than in the normal group (8.8 vs. 9.3 vs. 9.9, $p = 0.02$). MMSE was lower in the MCI and dementia groups than in the normal group (17.4 vs. 22.9 vs. 24.5, $p < 0.001$). GDS was higher but not significant in the MCI and dementia groups than in the

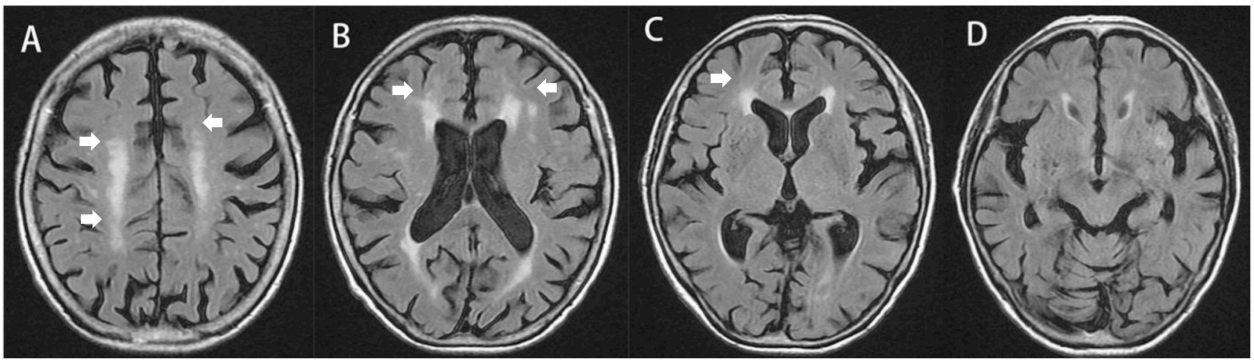

FIGURE 2 | Cholinergic pathways hyperintensities scale (CHIPS) scoring illustrated on T2-FLAIR MRI. The total score of this subject is 12. **(A)** Central semiovale: anterior (right = 1, left = 1, factor = 1, and total = 2); posterior (right = 2, left = 1, factor = 1, and total = 3), **(B)** Corona radiata: anterior (right = 1, left = 1, factor = 2, and total = 4); posterior (right = 0, left = 0, and total = 0); cingulate (right = 0, left = 0, and total = 0), **(C)** High external capsule: anterior (right = 1, left = 0, factor = 3, and total = 3), posterior (right = 0, left = 0, and total = 0); cingulate (right = 0, left = 0, and total = 0), **(D)** Low external capsule: anterior (right = 0, left = 0, and total = 0), posterior (right = 0, left = 0, and total = 0). White arrows highlights the abnormalities scored by CHIPS.

TABLE 1 | Demographic data.

	CDR = 0 n = 66 (36.5%)	CDR = 0.5 n = 88 (48.6%)	CDR = 1+ N = 27 (14.9%)	p-value	Group difference
Female (n, %)	35 (53.0%)	53 (60.2%)	14 (51.9%)	0.59	
Age	79.2 (4.2)	80.9 (3.8)	84.0 (5.0)	<0.001*	abc
Education	9.9 (2.2)	9.3 (1.6)	8.8 (1.7)	0.02*	c
MMSE	24.5 (3.3)	22.9 (2.9)	17.4 (5.2)	<0.001*	abc
GDS	3.6 (3.1)	4.4 (2.7)	5.4 (2.7)	0.18	c
CIDI-positive (n, %)	1 (1.5%)	5 (5.7%)	3 (11.1%)	0.049*	
MTA	3.1 (1.9)	4.0 (2.0)	5.8 (1.9)	<0.001*	abc
CHIPS	17.7 (16.5)	20.4 (16.2)	32.6 (20.6)	0.001*	bc
PVH	4.0 (1.8)	4.4 (2.0)	5.5 (2.1)	0.006*	c
DWMH	4.7 (2.6)	5.2 (2.2)	6.2 (2.2)	0.03*	c

*CDR, clinical dementia rating; MMSE, Mini–Mental State Examination; GDS, geriatric depression scale; CIDI, Composite International Diagnostic Interview; MTA, medial temporal atrophy; CHIPS, cholinergic pathways hyperintensities scale; PVH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity. Chi-square test was used for comparison of gender and CIDI-positive rate; one-way analysis of variance was used for comparison of other measures. *$p < 0.05$.*

[a]Group differences: CDR = 0 vs. CDR = 0.5 ($p < 0.05$, adjusted for multiple comparisons).

[b]Group differences: CDR = 0.5 vs. CDR = 1+ ($p < 0.05$, adjusted for multiple comparisons).

[c]Group differences: CDR = 0 vs. CDR = 1+ ($p < 0.05$, adjusted for multiple comparisons).

normal group (5.4 vs. 4.4 vs. 3.6, $p = 0.18$). A significantly higher proportion of the MCI and dementia groups had a history of depressive episodes (11.1% vs. 5.7% vs. 1.5%, $p = 0.049$). More atrophy of the medial temporal lobe was noted in the MCI and dementia groups (5.8 vs. 4.0 vs. 3.1, $p < 0.001$). Higher scores were obtained for CHIPS-rated WMHs in the MCI and dementia groups (32.6 vs. 20.4 vs. 17.7, $p = 0.001$). Higher scores were obtained for PVH-rated WMHs in the MCI and dementia groups (5.5 vs. 4.4 vs. 4.0, $p = 0.006$). Higher scores were obtained for DWMH-rated WMHs in the MCI and dementia groups (6.2 vs. 5.2 vs. 4.7, $p = 0.03$).

Comparison of Subjects with and without a History of Depression

Among our subjects, a lower proportion of women had a history of depression (22.2% vs. 58.1%, $p = 0.043$). No differences were observed in age, education, MMSE, and GDS between the depressed and nondepressed groups (**Table 2**). CDR was significantly higher in subjects with a history of depression (0.9 vs. 0.4, $p = 0.046$) (**Figure 3**). A smaller hippocampus was not found in these subjects (4.0 vs. 3.9, $p = 0.898$). No significant differences were observed in WMHs rated using CHIPs, PVH, or DWMH.

Comparison of Subjects in and Not in a Depressive State

Of 181 subjects, 72 (39.7%) were defined as being in a depressive state (GDS $\geq$ 5). The proportion of women was not different between the depressed and nondepressed group (54.2% vs. 57.8%, $p = 0.649$). No differences were observed in age and education between the groups. Subjects with depression exhibited lower MMSE scores (21.6 vs. 23.3, $p = 0.008$) and higher CDR scores (0.6 vs. 0.3, $p = 0.004$), and a higher proportion of subjects had a history of depression (9.7% vs. 1.8%, $p = 0.031$). A higher proportion of dementia cases were also noted in the depressed group (22.2% vs. 10%). Subjects in a depressive state exhibited more atrophy of the medial temporal lobe (4.4 vs. 3.7, $p = 0.036$). Correlation analysis revealed that GDS scores were

TABLE 2 | Comparison of subjects with and without a history of depression.

	With (CIDI-positive) $n = 9$	Without (CIDI-negative) $n = 172$	*p*-value
Female (*n*, %)	2 (22.2%)	100 (58.1%)	0.043*
Age	80.5 (3.7)	80.8 (4.4)	0.854
Education	10.0 (2.3)	9.4 (1.9)	0.519
MMSE	22.3 (5.4)	22.7 (4.1)	0.843
GDS	6.0 (2.3)	4.2 (2.9)	0.054
CDR	0.9 (0.9)	0.4 (0.5)	0.046*
CDR-SOB	4.0 (5.2)	2.2 (3.1)	0.105
MTA	4.0 (2.0)	3.9 (2.1)	0.898
CHIPS	22.4 (20.1)	21.1 (17.6)	0.858
PVH	4.7 (2.5)	4.4 (1.9)	0.744
DWMH	5.3 (2.3)	5.1 (2.4)	0.864

*CDR, clinical dementia rating; CDR-SOB, sum of boxes of clinical dementia rating scale; MMSE, Mini–Mental State Examination; GDS, geriatric depression scale; CIDI, Composite International Diagnostic Interview; MTA, medial temporal atrophy; CHIPS, cholinergic pathways hyperintensities scale; PVH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity. Chi-square test was used for comparison of gender and CIDI-positive rate; nonparametric test (Mann–Whitney U-test) was used for comparison of other measures. *p < 0.05.*

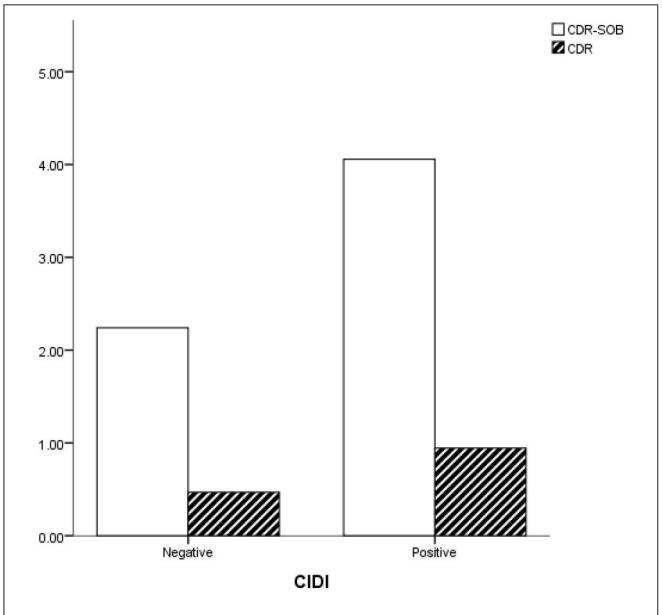

FIGURE 3 | Subjects with a history of depression (CIDI-positive) showed higher CDR and CDR-SOB scores than did those without it.

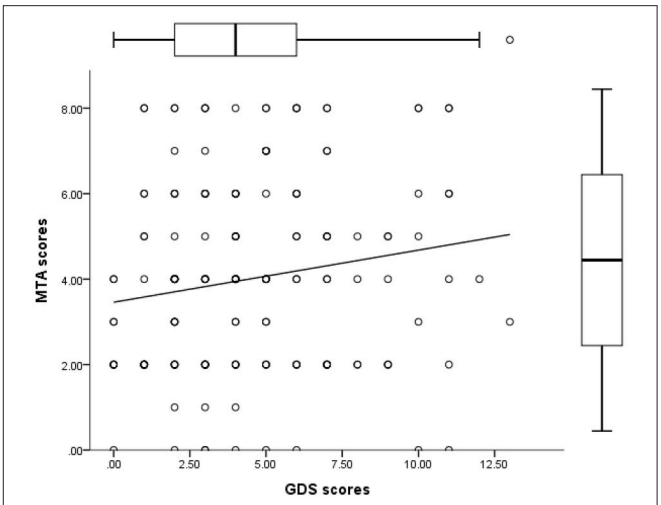

FIGURE 4 | Scatterplot showing that MTA scores were positively correlated with GDS scores ($r = 0.193$, $p = 0.009$).

TABLE 3 | Comparison of subjects with and without late-life depression.

	Depressed (GDS ≥ 5) $n = 72$	Nondepressed (GDS ≤ 4) $n = 109$	*p*-value
Female (*n*, %)	39 (54.2%)	63 (57.8%)	0.649
Age	81.4 (4.3)	80.3 (4.4)	0.123
Education	9.4 (1.7)	9.5 (2.0)	0.616
MMSE	21.6 (4.8)	23.3 (3.5)	0.008*
CDR score	0.6 (0.6)	0.3 (0.5)	0.004*
0	17 (23.6%)	49 (45%)	0.029*
0.5	39 (54.2%)	49 (45%)	
1+	16 (22.2%)	11 (10%)	
CIDI-positive (*n*, %)	7 (9.7%)	2 (1.8%)	0.031*
MTA	4.4 (2.3)	3.7 (2.0)	0.036*
CHIPS	23.5 (19.0)	19.6 (16.6)	0.148
PVH	4.7 (2.1)	4.3 (1.9)	0.196
DWMH	5.4 (2.2)	5.0 (2.5)	0.260

*CDR, clinical dementia rating; MMSE, Mini–Mental State Examination; GDS, geriatric depression scale; CIDI, Composite International Diagnostic Interview; MTA, medial temporal atrophy; CHIPS, cholinergic pathways hyperintensities scale; PVH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity. Chi-square test was used for comparison of gender and CIDI-positive rate; Student's t-test was used for comparison of other measures. *p < 0.05.*

positively correlated with MTA scores (**Figure 4**). Higher scores were obtained for WMH measured using different visual rating scales, namely CHIPS, PVH, and DWMH, in depressive subjects, but these scores were not statistically significant (**Table 3**).

DISCUSSION

Summary of Results

The prevalence of dementia in our study population was 14.9%. This finding is consistent with that of a previous study in the old-old population in Japan (Meguro et al., 2012). In our population, 4.9% had a history of depression, and 39.7% had depressive symptoms (based on screening results involving the GDS). Direct comparison of subjects with and without a history of depression revealed that more men had a history of depression, and subjects with a history of depression had a worse clinical dementia state (**Table 2**). Subjects with depressive symptoms had lower MMSE scores, a worse clinical dementia state, and a smaller hippocampus (**Table 3**).

Limitations

In this study, the number of cases was relatively small; thus, some positive results may have been overlooked because of a lack of statistical power. Because this was a community-based cross-sectional study, we did not further diagnose dementia subtypes in our patients. In the future, a longitudinal follow-up of these

TABLE 4 | Clinical data of nine subjects with a history of depressive episodes.

Case	Age	Gender	CDR	GDS	MDE	MMSE
1	78	Male	0.5	2	Negative	26
2	87	Male	3	6	Positive	16
3	79	Female	0.5	5	Positive	28
4	80	Male	0.5	6	Negative	27
5	74	Male	0	4	Positive	26
6	85	Male	1	9	Positive	20
7	80	Male	2	8	Negative	12
8	81	Female	0.5	5	Negative	22
9	81	Male	0.5	9	Negative	24

CDR, clinical dementia rating; MMSE, Mini–Mental State Examination; GDS, geriatric depression scale; MDE, major depressive episode.

subjects may provide more information. Another limitation is that we did not record the age of onset for the depressive episodes. Early- and late-onset depressive episodes may have different implications for our findings.

Lifetime History of Depression in Old-Old Population

Our study findings suggested that a lifetime history of depression is associated with a worse clinical dementia state in the old-old population. Eight of nine (88.9%) subjects with a history of depression were clinically defined as having MCI or dementia (**Table 4**). The lower prevalence of a history of depression compared with that in Western countries and the higher prevalence of a history of depression in men are both characteristic features of Japan (Ishikawa et al., 2016). Most previous studies have linked the history of depression to late-life vascular dementia (Hébert et al., 2000; Brunnström et al., 2013) or white matter changes (Duffy et al., 2014). However, in this study, more WMH was not detected in any subjects with a history of depression. Moreover, a smaller hippocampus was not found in any subject with a history of depression. This finding is similar to that of a previous study of Alzheimer disease (Brunnström et al., 2013). Based on our study findings, a smaller hippocampus and white matter changes may not be the common origins of lifetime depressive episodes and dementia. Although it is possible that our sample size is too small to demonstrate statistical significance, other causes might still explain both conditions.

Late-Life Depression and Dementia

Another major point of this study is that the findings increase understanding of the relationship between late-life depression and dementia. Subjects with senile depression exhibited poor cognitive performance and more atrophy of the medial temporal lobe than did those without senile depression. The relationship between chronic depression and a smaller hippocampus has long been recognized. A previous longitudinal study even proved that late-life depression leads to hippocampal decline but not vice versa (den Heijer et al., 2011). Our target population was older than those of previous studies. Thus, we could comprehensively observe the consequences of senile depression. Furthermore, in our target population, subjects with depression had a higher prevalence of dementia and lower cognitive performance than did those without depression.

By contrast, vascular risk factors or widespread WMH changes have always been assumed to be among the possible causes of late-life depression. Most studies have reported more WMHs in people with late-life depression (Fujishima et al., 2014). In our study, although subjects with depression showed higher WMH scores (rated using CHIPS, PVH, and DWMH), the findings were not statistically significant (**Table 3**). However, this result might be because our subjects represent the old-old population, and white matter changes are also a part of the aging process (Gunning-Dixon et al., 2009). We might have needed more cases to reach statistical significance. Most recent studies support the notion that senile depression is a prodromal symptom of vascular dementia or all-cause dementia. Based on our findings, depression in the old-old population is related to lower cognitive performance and, potentially, future dementia development. However, to establish such a temporal relationship, a longitudinal study should be conducted in the future.

In conclusion, we found lifetime history of depression do have some effects on dementia onset in old-old population. Participants with history of depressive episodes have higher CDR scores. However, we didn't find them with more atrophy medial temporal lobe or more WMHs. In old-old population, lifetime depressive episodes may have significant effects on their clinical condition without structural changes. Previous reports have revealed more neuropathological changes in AD patients with lifetime history of major depression (Rapp et al., 2006). Our reports further support the importance of lifetime history of depression in old-old population. On the other hand, depressive state in this group of people related to smaller hippocampus. However, we didn't find depressive state significantly related to more WMHs.

AUTHOR CONTRIBUTIONS

YL: analyzing the data and writing the manuscript KM: design the study and collecting and analyzing the data KN, KA, MN, TS: collecting the data SN, MM, NK: discussion

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frontiers in Aging Neuroscience

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A Novel Stress-Diathesis Model to Predict Risk of Post-operative Delirium: Implications for Intra-operative Management

*Renée El-Gabalawy[1,2], Ronak Patel[2], Kayla Kilborn[1], Caitlin Blaney[1], Christopher Hoban[1], Lawrence Ryner[3], Duane Funk[1], Regina Legaspi[1], Joseph A. Fisher[4], James Duffin[5], David J. Mikulis[6] and W. Alan C. Mutch[1,7]**

[1] Department of Anesthesia and Perioperative Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada, [2] Department of Clinical Health Psychology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, [3] Department of Physics and Astronomy, Faculty of Science, University of Manitoba, Winnipeg, MB, Canada, [4] Department of Anesthesia, Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [5] Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [6] Department of Medical Imaging, Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [7] Canada North Concussion Network, Winnipeg, MB, Canada

Introduction: Risk assessment for post-operative delirium (POD) is poorly developed. Improved metrics could greatly facilitate peri-operative care as costs associated with POD are staggering. In this preliminary study, we develop a novel stress-diathesis model based on comprehensive pre-operative psychiatric and neuropsychological testing, a blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) carbon dioxide (CO_2) stress test, and high fidelity measures of intra-operative parameters that may interact facilitating POD.

Methods: The study was approved by the ethics board at the University of Manitoba and registered at clinicaltrials.gov as NCT02126215. Twelve patients were studied. Pre-operative psychiatric symptom measures and neuropsychological testing preceded MRI featuring a BOLD MRI CO_2 stress test whereby BOLD scans were conducted while exposing participants to a rigorously controlled CO_2 stimulus. During surgery the patient had hemodynamics and end-tidal gases downloaded at 0.5 hz. Post-operatively, the presence of POD and POD severity was comprehensively assessed using the Confusion Assessment Measure –Severity (CAM-S) scoring instrument on days 0 (surgery) through post-operative day 5, and patients were followed up at least 1 month post-operatively.

Results: Six of 12 patients had no evidence of POD (non-POD). Three patients had POD and 3 had clinically significant confusional states (referred as subthreshold POD; ST-POD) (score $\geq$ 5/19 on the CAM-S). Average severity for delirium was 1.3 in the non-POD group, 3.2 in ST-POD, and 6.1 in POD (F-statistic $=$ 15.4, $p < 0.001$). Depressive symptoms, and cognitive measures of semantic fluency and executive functioning/processing speed were significantly associated with POD. Second level analysis revealed an increased inverse BOLD responsiveness to CO_2 pre-operatively in ST-POD and marked increase in the POD groups when compared to the non-POD group. An association was also noted for the patient population to manifest leucoaraiosis as

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***Correspondence:**
W. Alan C. Mutch
wacmutch@shaw.ca

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assessed with advanced neuroimaging techniques. Results provide preliminary support for the interacting of diatheses (vulnerabilities) and intra-operative stressors on the POD phenotype.

Conclusions: The stress-diathesis model has the potential to aid in risk assessment for POD. Based on these initial findings, we make some recommendations for intra-operative management for patients at risk of POD.

Keywords: post-operative delirium, neuropathophysiology, peri-operative care, neuropsychological, stress-diathesis, neuroimaging

INTRODUCTION

Post-operative delirium (POD) remains a poorly understood and highly variable neuropsychiatric syndrome characterized by neurocognitive dysfunction, which can include fluctuating disturbances in attention, awareness, thinking, and psychomotor behavior that frequently manifests in the hours or days following surgery. Proper classification of the condition remains problematic and may encompass a spectrum of acute confusional states and low-grade encephalopathic states (Martins and Fernandes, 2012). This has been referred to as subsyndromal or subthreshold POD in prior research and more recently described as Attenuated Delirium Syndrome in the Diagnostic and Statistical Manual of Mental Disorder 5th Edition (DSM-5; American Psychiatric Association, 2013). Indeed, recent research assessing a spectrum of severity of POD suggests that poor outcomes are associated with confusional states not meeting full POD criteria (Inouye et al., 2014a), emphasizing the importance of a graded severity assessment. Risk prediction, prevention and optimal peri-operative course to minimize these related problems are largely unknown. The individual and societal costs of management of these problems are substantial (Young and Inouye, 2007; Dasgupta and Hillier, 2010) and the health care costs soar into the billions of dollars annually (Leslie et al., 2008). POD has been conceptualized as a "disease of the elderly" because of its high prevalence in late life and that older adults with dementing disorders and/or vascular compromise are particularly prone to the risks of POD (Beals et al., 2003; Olney et al., 2004; Baranov et al., 2009; Lei et al., 2014; Strøm et al., 2014; Fong et al., 2015). Historically, the expression of POD has hinged on the concept that anesthetic agents may be toxic to brain tissue. This study proposes a novel conceptualization of POD that moves away from the contribution of the anesthetic agents themselves to critically examine the conduct of anesthesia, and how this management may interact with existing risks, to impact the vulnerable brain. We provide preliminary data to support this novel hypothesis.

Recently big data retrospective clinical studies and meta-analyses would suggest that neurotoxicity related to anesthetic exposure does not predict POD (Mason et al., 2010). Prior investigations have been largely driven by preclinical animal models, and neuronal dropout indicative of anesthetic neurotoxicity may not translate to POD in humans (Jevtovic-Todorovic, 2016). Further, in recent years, clinical studies investigating neuroprotection of anesthetic agents have also been criticized because of the questionable quality of these trials (Ishida et al., 2014). Prospective studies to examine anesthetic depth or the potential protective effects of chosen agents such as ketamine have resulted in null findings (e.g., Avidan et al., 2017) and findings are mixed in the research that does exist. There is an evident need to investigate other potential mechanisms.

Our partial understanding of POD is partly attributable to the fact that research to date has been limited in its comprehensiveness. First, there has been only partial use of major advancements in neuroimaging techniques. A recent review of the literature published in the *Lancet* (2014) stresses the importance of these advanced neuroimaging techniques for shedding light on the pathophysiological complexities that seem to exist for POD (Inouye et al., 2014b). Preliminary evidence from case series have suggested that cerebral blood flow may play an important role in POD (Yokota et al., 2003; Fong et al., 2006). In one recent retrospective study, abnormalities in cerebral blood flow were identified as contributing to neurological complications post-operatively including POD (Xu et al., 2015), yet this has not been in a sophisticated manner. As previously indicated, another shortcoming of prior research relates to a limited scope in POD nosology as a discrete entity. The National Institute of Mental Health initiated the Research Domain Criteria to urge researchers to conceptualize mental disorders more broadly outside the confines of the DSM with a focus on symptomatology, model mental illnesses as brain disorders and identify syndromes based on pathophysiological findings (Insel et al., 2010). This emphasizes the importance of broadening current understanding of POD and examining POD on a spectrum of severity to include acute confusional states and low-grade encephalopathic states.

In this preliminary study we document our comprehensive approach to establish a stress-diathesis (vulnerability) multifactorial model predictive of POD in patients having major surgery. The concept of a stress-diathesis model has been used widely in psychological research accounting for the dynamic interplay between pre-existing dispositions or vulnerabilities and the role of environmental stressors acting as catalysts in the expression of a particular condition. A large body of research has established critical pre-operative risk factors in adults such as pre-operative cognitive dysfunctions (Dasgupta and Dumbrell, 2006; Inouye et al., 2014b; Jones et al., 2016), history of psychiatric illness, and illicit drug use (Inouye et al., 2014b; O'Sullivan et al., 2014). These risk factors have all been shown to be associated with neurodegenerative processes

including cerebrovascular dysfunction (Sprooten et al., 2017). The intra-operative period characterizes the stressor in this model, which has also been largely overlooked with respect to a close examination of intra-operative course including changes in critical hemodynamic factors and management of gas exchange during mechanical ventilation, which is hallmark in both surgical and intensive care settings.

This study aims to comprehensively examine critical vulnerability factors established in prior research including all major domains of cognitive functioning through neuropsychological testing and psychiatric history. We also included an examination of the pre-operative brain using blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) while patients underwent regulated CO_2 exposure (referred to as the "CO_2 stress test") to act as a proxy for end-tidal CO_2 stress during surgery where a paradoxical vasodilatory response may reduce cerebral blood flow affecting vulnerable regions of the brain (referred to as intracranial steal; see **Supplemental Data Sheet 1** and **Supplemental Figures 1A,B** for a description of the approach used in this study). With respect to the proposed stressor, we have monitored intra-operative hemodynamics, end-tidal gas tensions and cerebral oximetry with high fidelity. Finally, we conducted a comprehensive assessment of POD using the Confusion Assessment Method-Severity (CAM-S) to yield continuous scoring to enable identification of both "subthreshold" and full manifestations, and included a follow-up assessment at least 1 month post-operatively. A preliminary predictive model is constructed and recommendations for patient management are advanced.

METHODS

This study was approved by the Biomedical Research Ethics Board (BREB) of the University of Manitoba. This trial is registered at clinicaltrials.gov as NCT02126215.

Patients who were undergoing high-risk surgeries requiring a post-operative stay were approached to participate in the study through the Pre-Anesthesia Clinic (PAC) of the Health Sciences Centre at the Max Rady College of Medicine in Winnipeg, MB. Witnessed informed consent was obtained from each patient. Exclusion criteria included simultaneous planned carotid endarterectomy, carotid stenosis—if previously documented, contraindications to MRI including claustrophobia, and known chronic obstructive lung disease with CO_2 retention. At the time of consent, patients completed psychiatric symptom measures (described below). Patients were seen pre-operatively in the week prior to surgery for comprehensive neuropsychological testing followed immediately by the MRI BOLD CO_2 stress test. Patients received a $50 gift card that included coverage for transportation and parking during their pre-operative visit for participation in the study. A trained psychometrist (PhD level clinical psychology graduate student) supervised by a registered Clinical Neuropsychologist administered a battery of neuropsychological tests over the span of approximately 1 hour. Subsequently, the MRI BOLD CO_2 stress test was initiated. Patients returned for their scheduled surgery. There were no changes to standard surgical procedures; trained research personnel collected intra-operative data. Following surgery, trained research personnel blinded to pre-operative performance on all assessments conducted daily POD assessments for up to 5 post-operative days including day 0 (day of surgery). Patients were subsequently contacted via phone at least 1 month post-operatively and asked about their cognitive functioning since their surgery.

Diathesis Assessments

Pre-operative Psychiatric and Neuropsychological Assessments

Upon initial recruitment in PAC, patients completed the validated Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) to assess depressive symptoms and the Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006) to assess anxiety symptoms, and self-reported on psychiatric disorder diagnoses previously made by health professionals. They also reported on their history of illicit drug use. Patients were flagged if they were clinically significant on the PHQ-9 and GAD-7 ($\geq$10), reported a psychiatric diagnosis, or who indicated illicit drug use in 2 weeks prior to their surgery.

For neuropsychological testing, attention was assessed using Trails A and Weschler Adult Intelligence Scale (WAIS)-IV Digit Span; information processing speed using WAIS-IV Digit Symbol Coding; verbal memory using Hopkins Verbal Learning Test-Revised; visual construction, planning and organization using Rey's Complex Figure (copy trial); visual memory using Rey's Complex Figure (immediate recall trial); executive functioning/processing speed using Trails B and Delis-Kaplan Executive Function System (DKEFS) Color Word Interference; verbal and semantic fluency using F-A-S and Animal Fluency; spatial skills using CLOX I (free draw) and II (copy); and global cognitive and mental status using the Mini-Mental Status Examination (MMSE). Raw scores were converted to scaled scores and standard scores (dependent on measure assessed). Patients also completed a baseline POD assessment, described below.

Pre-operative Neuroimaging and CO_2 Stress Test

The CO_2 stress test was conducted during neuroimaging where all participants had model-based prospective end-tidal (MPET) CO_2 targeting achieved by precise delivery of CO_2 at a fixed concentration using a sequential breathing circuit regulated by a computerized gas-blender (RespirAct^{TM}, Thornhill Research Inc., Toronto, ON) (Slessarev et al., 2007). This device allows precise manipulation of end tidal CO_2 levels under iso-oxic conditions (see **Supplemental Data Sheet 1** for a description of the terms related to gas exchange used in this study)—and a target end tidal O_2 = 115 mmHg. Monitoring during the imaging period included continuous heart rate and pulse oximetry and non-invasive blood pressure (BP) at 3-min intervals.

All images were acquired using a Siemens Verio 3.0T MR scanner with a 12-channel phased-array head coil. The MRI

protocol consisted of baseline anatomical imaging including sagittal 3D T1 magnetization-prepared rapid gradient-echo (MPRAGE) (whole brain coverage; matrix: 256 × 256; slice thickness: 2.2 mm; no interslice gap), axial fluid-attenuated inversion recovery (FLAIR), axial gradient recalled echo planar images (EPI GRE) sequences, and continuous BOLD EPI with MPET. The breathing sequence during BOLD imaging consisted of a triple box-car hypercapnic stimulus (see **Supplemental Figure 1A** for the sequence used). A video is shown in **Supplemental Video 1** demonstrating the dynamic response of the brain regionally to changes in end-tidal CO_2 tension.

BOLD MRI data was acquired with a T2*-weighted single-shot gradient echo pulse sequence with echoplanar (EPI) readout (field of view: 24 × 24 cm; matrix: 64 × 64; TR: 2000 ms; TE: 30 ms; flip angle: 85°; slice thickness: 5.0 mm; interslice gap: 2.0 mm; voxel size 3.75 × 3.75 × 6.0 mm; number of temporal frames = 330). A 30-s lead in for BOLD imaging was undertaken for equilibration and these images were discarded from analysis. The total duration of the MRI assessment was approximately 25 min.

Stressor Assessments

Intra-operative Assessments

No management constraints were placed on the patient's anesthetic approach. Where appropriate, regional anesthetic supplements were undertaken (nerve blocks or epidurals). All patients received a general anesthetic—either sevoflurane or desflurane as volatile agent in air:O_2. As per standard of care, no patient was administered N_2O. All patients received intravenous supplements including propofol and midazolam for induction and muscle relaxants as required. All were endotracheally intubated and mechanically ventilated. All patients had arterial cannulation to record blood pressure continuously, electrocardiography (ECG) monitoring to record heart rate, and infra-red sensors were applied to the forehead bilaterally to measure frontal lobe oxygen saturation (ForeSight monitor). Hemodynamics, end-tidal gas tensions (O_2, CO_2 and anesthetic vapor) were recorded at 0.5 hz using a data acquisition system and stored on a laptop computer. The data stream recorded at 0.5 hz included heart rate, systolic, diastolic and mean blood pressure, respiratory rate, tidal volume, end-tidal O_2 and CO_2, end-tidal anesthetic vapor, right, left and mean cerebral oxygen saturation. The duration of time in the operating room was also recorded. Concatenated data were examined and we report on mean arterial pressure greater than or less than 60 mmHg, end-tidal CO_2 delta greater than or less than 5 mmHg, end-tidal vapor concentration greater than or less than one minimum alveolar concentration (MAC)—age adjusted, cerebral saturation greater than or less than 60% and duration of procedure greater than or less than 120 min. As well, hemodynamic and end-tidal data were further examined. The median value for mean blood pressure and end-tidal CO_2 were assessed. For blood pressure, the pressure below the 10th percentile and above the 90th percentile, and the duration above and below these limits, were determined for each patient as an index of hemodynamic instability. As an index of variability in intra-operative end-tidal CO_2 control, the duration above or below the median CO_2 by ± 5 mmHg for the conduct of the intra-operative course was determined for each patient—a reflection of the CO_2 delta examined by the MRI BOLD CO_2 stress test employed. The duration of cerebral saturation below 60% O_2 saturation was also collated. At the end of their surgical procedure all patients were initially monitored in the recovery room and then transferred either to the surgical intensive care, or the inpatient surgical wards. Both intra-operative and total narcotic dose over the course of the hospital stay was calculated for each patient with dosages of the various narcotics used converted to morphine equivalents in mg. The data stream was processed, collated with Excel, and transferred to SPSS for analysis.

Post-operative Assessment for Delirium

A trained blinded interviewer conducted the CAM-S, a structured 10-15 min clinical interview, to assess the presence and severity of POD. In cases where the patient was intubated or could not complete the extended CAM-S, the briefer CAM-ICU was administered. With the exception of fluctuation, which is identified as mild (score of 0) or marked (score of 1), all other symptoms are identified as absent (0), mild (1) or marked (2). The total severity score was based on a sum score that could range from 0 through 19. In this study, we report the *peak* post-operative severity score for each patient throughout their inpatient stay and the *average* severity score up to 5 post-operative days (unless discharged prior to 5 days). A diagnosis of full POD was based on the presence of either acute onset of change or symptom fluctuation in mental status, inattention, and either disorganized thinking or altered level of consciousness, in line with prior research. In this sample, full POD was associated with peak severity scores on at least 1 post-operative day that ranged from 8 to 14. Subthreshold delirium (ST-POD) was defined as those not meeting full criteria but displayed elevated severity scores (≥5) on the POD severity long form on at least 1 post-operative day. This clinically significant cutoff has been found to be associated with higher risk of increased length of stay, increased healthcare costs, and post-operative admittance to nursing homes, functional and cognitive decline, and death within 90 days post-operatively compared to lower scores (Inouye et al., 2014a). Patients with ST-POD also met a large proportion of criteria for full POD with the exception of one or two items. For patients who did not want to complete the extended interview, the short severity form was offered and these scores were subsequently weighted on the same metric as the long form. All patients were followed up by phone by a research assistant at least 1 month post-operatively and asked if the patient or a loved one of the patient noticed if there *"was a short or long period of time after you got home that you felt your thinking had changed. For example, this could be changes in your ability to focus your attention and/or being able to keep track of what is being said to you, difficulty staying on one subject while speaking, feeling confused, or problems remembering things. This could even be seeing or hearing things that weren't really there."* Responses are descriptively reported.

Statistical Analyses

Standard preprocessing of MRI EPI output was accomplished with statistical parametric mapping version 8 (SPM8) software, including batch processing by an SPM toolbox and custom written in-house MatLab scripts. The preprocessing included re-alignment of images, slice time correction, co-registration with the MPRAGE images, re-slicing to the MPRAGE dimensions for both approaches, smoothing and normalization into Montreal Neurological Institute (MNI) space and inclusive masking to assess gray and white matter distribution. Motion artifact was examined. Studies were rejected if motion over the conduct of the study period was greater than 3 mm in any plane. BOLD imaging was processed as 1st and 2nd level analysis by SPM. intra-operative data were concatenated and binned on a minute-by-minute basis.

The structural neuroimaging components from each study were reviewed by a board-certified neuro-radiologist, who indicated a Fazekas score for each patient (see below).

Other data were analyzed using SPSS. Bivariate correlations examined the relationship between cognitive summary scores and psychiatric severity scores as indicated by PHQ-9 and GAD-7 with continuous severity POD measures. If significant results were indicated, we conducted a bivariate linear regression model followed by a model controlling for age, education, sex and pre-operative baseline POD severity. We also conducted analyses of variance to examine mean score differences across primary diathesis and stress factors among those classified as non-POD, ST-POD, and full POD. Finally, to examine the within subjects change from pre-operative CO_2 delta during the stress test to intra-operative CO_2 delta by the between-subjects POD groups, we conducted a repeated measures analysis of covariance including age, education and sex as covariates, and additionally: (1) identified cognitive and psychiatric diathesis factors, (2) hypercapnic and inverse hypercapnic voxel responses in gray and white brain matter, and (3) contributory intra-operative factors. Because of restricted sample size, results are shown graphically, and trends are only discussed descriptively.

RESULTS

Patient Characteristics

Twelve patients completed the protocol. A total of 30 patients undergoing high-risk surgeries were approached in the PAC for enrollment. Thirteen were unwilling to participate, leaving 17 who consented. The majority of patients that were approached and unwilling to participate lived in rural Manitoba, and could not make an additional trip to Winnipeg prior to their surgery. Of the remaining, 5 patients were excluded; 2 had contraindications to the MRI; 1 had surgery canceled; 1 had a scheduling conflict for MRI scan time; and 1 was too nervous to be scanned.

Individual patient characteristics are shown in **Table 1** (sociodemographic and diathesis factors for all participants) and **Table 2** (intra-operative stress factors for all participants). The mean age of the entire sample was 62 ± 10 years and mean education was 13 years ± 2. There were 7 males and 5 females. The mean duration of surgery was 221 ± 39 min. In 6 of 12 patients the mean BP fell below 60 mmHg on at least one occasion for a minimum of 1 min. In 2 of 12 the cerebral saturation was less than 60% for a minimum of 1 min. The mean CO_2 delta was 13.2 ± 3.0 mmHg.

CO_2 MRI Stress Test

The end-tidal gas control for each patient and the comparison between the non-POD patients and the combined POD and ST-POD patients is shown in Supplementary Material.

A comparison between a patient deemed low risk and a patient high risk for POD following MRI BOLD CO_2 stress testing is shown in **Figures 1A,B**. The expected response to the hypercapnic stimulus at the $p = 0.001$ level is shown in the hot voxels (shades of orange). The inverse response to the hypercapnic stimulus—that is a decrease in BOLD signal with an increase in CO_2 or vice versa is shown by the cold voxels (shades of blue). See the **Supplemental Figures 1A,B** for a full description of the approach. The blue voxels are indicative of regions of intracranial steal.

Figure 2A demonstrates 2nd Level Analysis in SPM comparing the non-POD group and ST-POD group. The hot voxels represent where the BOLD response to CO_2 is significantly more pronounced in the non-POD group. The cold voxels indicate where the BOLD response is significantly less in ST-POD. **Figure 2B** demonstrates 2nd Level Analysis in SPM comparing non-POD group and the POD group. The hot voxels represent where the BOLD response to CO_2 is significantly more pronounced in the non-POD or control group. The cold voxels indicate where the BOLD response is significantly less in the POD group. The color bar indicates significant *t*-values at the $p = 0.05$ level in both circumstances.

Axial FLAIR Imaging

Axial FLAIR images were examined for evidence of leucoaraiosis—a white matter lesion associated with BOLD image CVR changes and later life dementia (Sam et al., 2016a,b). **Figure 3A** demonstrates an axial FLAIR image of one of the non-POD patients and **Figure 3B** a POD patient. The **Figure 3B** shows areas of hyperintensity in the periventricular regions and in the deep white matter.

Neuropsychological and Psychiatric Factors

Table 1 displays percentiles of each significant neuropsychological factor, and the presence or absence of psychiatric illness across all participants. Not shown, bivariate correlations revealed that certain neuropsychological measures, including Animal Fluency scaled score ($r = -0.90$, $p < 0.001$), DKEFS Color Word Interference Condition 1 ($r = -0.76$, $p = 0.006$) and Condition 2 ($r = -0.73$, $p = 0.01$) scaled scores, and CLOX 1 z-score ($r = -0.83$, $p = 0.02$) were significantly correlated with peak POD score, such that worse scores on these measures pre-operatively were associated with higher post-operative peak POD scores. Bivariate correlations also indicate Animals ($r = -0.81$, $p = 0.002$) and DKEFS Color Word Interference Condition 1 ($r = -0.76$, $p = 0.007$) and 2 ($r = -0.70$, $p = 0.002$) were significantly associated with average POD severity score. Linear regressions corroborated

TABLE 1 | Sociodemographic and diathesis factors among each participant.

				Neuropsychological testing		Voxel counts								
Pt	**Age**	**Sex**	**Psychiatric disorder**	**Semantic fluency (Per)**	**Information processing (Per)**	**Gray + White Matter Type 1**	**Gray + White Matter Type 2**	**Gray matter Type 1**	**Gray Matter Type 2**	**White Matter Type 1**	**White Matter Type 2**	**Total count**	**Fazekas score**	**Delirium**
1	59	F	1	45	37	0	1	0	0	0	1	2	0	POD
2	72	M	0	86.5	43.5	0	0	0	0	0	0	0	0	NON-POD
3	64	M	0	50	63	0	0	0	0	0	0	0	0	NON-POD
4	75	M	0	82	69	1	0	1	0	1	0	3	1	ST-POD
5	60	F	0	50	56.5	1	1	1	1	1	1	6	1	ST-POD
6	56	F	1	55	16	1	0	1	0	1	0	3	0	ST-POD
7	66	M	1	1	1	1	0	1	0	0	1	3	2	POD
8	58	M	0	81	63	0	0	0	0	0	0	0	0	NON-POD
9	77	F	0	84	20	1	0	1	0	1	0	3	2	NON-POD
10	51	F	0	1	N/A	0	0	0	0	0	0	0	0	POD
11	43	M	0	45	50	0	0	0	1	0	0	1	0	NON-POD
12	63	M	0	81	75	0	1	0	0	0	1	2	1	NON-POD

Pt, patient number; 1, yes; 0, no; Per, percentile; N/A, missing; POD, post-operative delirium; ST, subthreshold. Psychiatric disorder indicated in those with clinically significant levels of depressive or anxiety symptoms, reported diagnosis, or illicit drug use in past 2 weeks. Percentiles are reported for semantic fluency (standard score for Animals) and information processing (DKEFS Color Word Interference mean of standard score on condition 1 and 2). All voxel counts calculated at p = 0.001. Type 1 = response to hypercapnic stimulus (increased BOLD response); Type 2 = inverse response to hyperapnic stimulus (decreased BOLD response). Among voxel counts, 1 = <median for type 1 and >median for type 2 (non-normal); 0 = >median for type 1 and <median for type 2 (normal); total count = number of non-normal voxels.

TABLE 2 | Peri-operative stress factors among each participant.

	MAP				CO_2 Level								
Pt	**MAP < 60**	**<10th Per**	**>90th Per**	**Total**	**CO_2 delta**	**5 mmHg less**	**5 mmHg greater**	**Total**	**Mean MAC**	**Sat < 60%**	**Time < 60%**	**Length**	**Delirium**
1	0	12	11	23	9.1	0	4	4	1.1	0	0	107	POD
2	1	36	11	47	17.4	73	14	87	N/A	0	0	376	NON-POD
3	0	8	6	14	13.8	25	33	58	0.9	0	0	78	NON-POD
4	0	45	44	99	20	13	37	50	0.9	0	0	450	ST-POD
5	0	12	11	23	9.8	8	0	8	0.9	0	0	120	ST-POD
6	1	3	6	9	13.7	0	6	6	0.9	0	0	114	ST-POD
7	1	37	38	75	14.5	26	4	30	0.6	1	30	377	POD
8	1	27	27	54	12.4	1	1	2	1.0	0	0	284	NON-POD
9	1	6	5	11	N/A	N/A	N/A	N/A	N/A	0	0	61	NON-POD
10	1	19	18	37	13.2	7	0	7	0.6	1	94	192	POD
11	0	27	13	50	7.5	0	0	0	1.1	0	0	270	NON-POD
12	1	18	19	37	9.2	2	11	13	0.8	0	0	228	NON-POD

Pt, patient; N/A, missing; MAP, mean arterial pressure; Per, percentile; POD, post-operative delirium; MAC, minimum alveolar concentration; ST, subthreshold <10th Per = less than 10th percentile of median MAP for duration of procedure; >90th Per = greater than 90th percentile of median MAP for duration of procedure; 5 mm Hg Less = 5 mm Hg less than the median intra-operative CO_2 for the duration of the procedure; 5 mm Hg Greater = 5 mm Hg greater than the median intra-operative CO_2 for the duration of the procedure; Time < 60% = time in minutes the cerebral saturation was less than 60% oxygen saturation

these findings. Multiple linear regressions controlling for age, education, sex, and baseline CAM-S revealed that Animal Fluency ($\beta = -1.2$, $p < 0.001$), DKEFS Condition 1 ($\beta = -1.6$, $p = 0.003$) and Condition 2 ($\beta = -1.0$, $p = 0.01$) were significantly associated with peak POD score, but CLOX 1 was non-significant. Results were corroborated for multiple linear regressions with average delirium score as the dependent variable.

With respect to psychiatric factors, results revealed that PHQ-9 summary score was bivariately correlated to average delirium severity score ($r = 0.58$, $p = 0.049$). Adjusted linear regressions were non-significant.

Intra-operative Stress

Intra-operative stress is summarized in **Table 2** for each participant. Contributory trends emerged for the following

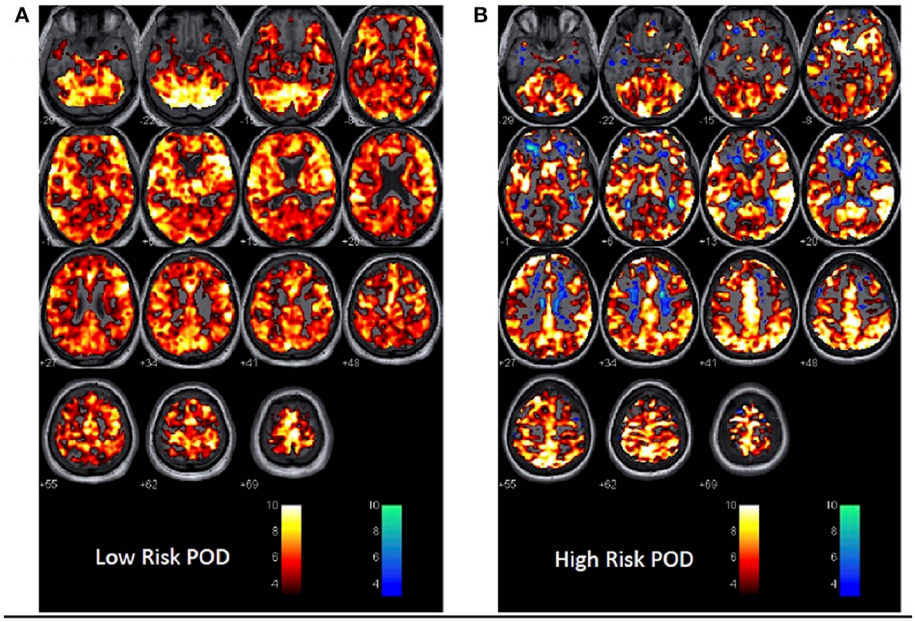

FIGURE 1 | 1st Level Analysis in SPM showing response to the CO_2 stress test in **(A)** a patient at low risk for POD.In this instance the expected response to the CO_2 stimulus as recorded during BOLD imaging is shown. A vigorous response to CO_2 is evident from the hot voxel response—shades of orange. The response at the $p = 0.001$ level occurred in 84% of whole brain parenchyma. The numbers below each image are the distance in mm above or below the anterior-posterior commissure. This patient was a non-POD outcome. The color bar is the *t*-value for fit to the general linear model from the SPM analysis. Voxels are colored if the *t*-value exceeded 3.11 in this instance. **(B)** A patient at risk of POD. Here there is less response to the hypercapnic signal—a 64% response to hypercapnia and now an inverse or intracranial steal signal shown in cold voxels—shades of blue. The inverse voxel count was 4.3% of the total count. This patient had a subthreshold POD outcome.

stressors—mean blood pressure less than 60 mmHg, end-tidal CO_2 delta greater than 10 mmHg, cerebral saturation less than 60% and surgical duration greater than 120 min. Anesthetic stress defined by these factors descriptively appear to contribute to POD outcomes, acting as either a catalyst in the case of few diathesis risk factors and high intra-operative stress, or a protective factor in the case of diathesis risk and low intra-operative stress. There were no significant differences in post-operative narcotic dosing intra-operatively or post-operatively between the 3 groups (shown in **Table 3**).

Stress-Diathesis Summary Findings

Table 3 demonstrates mean scores of primary variables associated with POD across the 3 POD groups. Significant differences in peak POD scores and average POD scores were demonstrated for non-POD, ST-POD, and full POD groups. Corroborating previous regression findings, results also indicated significant differences across POD groups for depressive symptoms, and percentile scores (displayed for interpretability) on semantic fluency and processing speed/executive functioning on neuropsychological testing. A chi-square analysis indicated a significant difference for cerebral saturation (SAT), indicating only those with full POD had cerebral SAT less than 60%.

Figures 4A-D demonstrates graphical results from the repeated measure analysis of covariance. The Y-axis in all graphs represents marginal means, and the X-axis represents pre-operative CO_2 delta as indicated by the stress test, and intra-operative CO_2 delta. **Figure 4A** includes age, sex, and education as covariates in the model, demonstrating larger intra-operative CO_2 delta for ST-POD and POD compared to non-POD. **Figure 4B** controls for sociodemographics, significant neuropsychological factors, and presence of a psychiatric disorder. As demonstrated, intra-operative stress is attenuated for the POD group, while maintaining significant diathesis CO_2 elevation pre-operatively. Intra-operative stress of CO_2 delta is significantly higher for ST-POD, than non-POD and POD groups. **Figure 4C** controls for sociodemographics, and pre-operative voxel count for gray and white matter in hypercapnic response and inverse hypercapnic responses. Controlling for this diathesis results in pre-operative elevation in CO_2 delta for ST-POD and POD groups relative to non-POD, and a risk gradient for intra-operative CO_2 delta, where ST-POD demonstrated the largest marginal mean, followed by POD, and non-POD. **Figure 4D** controls for socio-demographics and intra-operative stressors, results dramatically change where POD has higher intra-operative CO_2 delta marginal means compared to non-POD and ST-POD groups. **Figure 5** displays the proposed stress-diathesis model of POD and ST-POD incorporating these factors.

Post-operative Delirium Follow-up

All 12 patients were successfully reached at follow-up (time since surgery range = 1 to 6 months). In the non-POD group, 5 participants reported no change in thinking, and one discussed

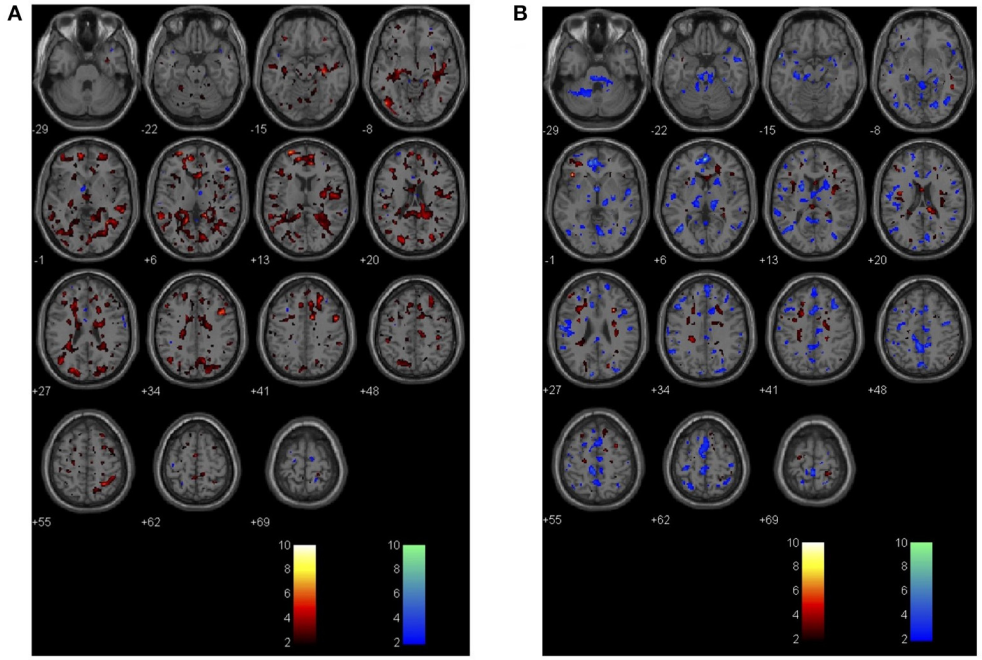

FIGURE 2 | (A) Demonstrates 2nd Level Analysis in SPM comparing the non-POD group ($n = 6$) and the subthreshold (ST) group ($N = 3$). The hot voxels represent where the BOLD response to CO_2 is significantly more pronounced in the non-POD or control group. The cold voxels indicate where the inverse BOLD response is significantly more in the ST group. The color bar is for $p = 0.05$ in this circumstance. **(B)** 2nd Level Analysis in SPM comparing the non-POD group ($n = 6$) and the POD group ($N = 3$). The hot voxels represent where the BOLD response to CO_2 is significantly more pronounced in the non-POD or control group. The cold voxels indicate where the inverse BOLD response is significantly more in the POD group. The color bar is for $p = 0.05$ in this circumstance.

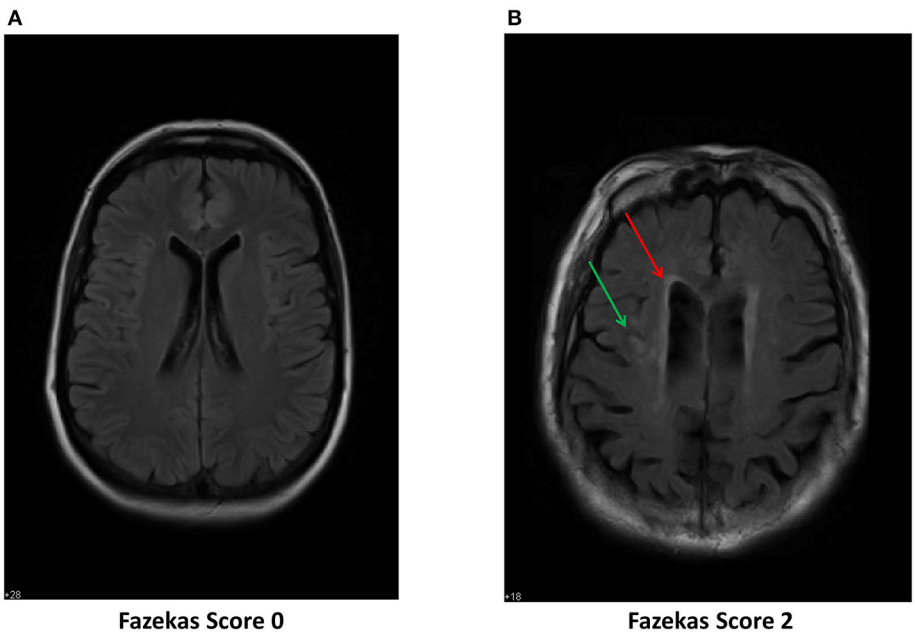

FIGURE 3 | Axial FLAIR images of two of the study patients. **(A)** Shows normal white matter imaging. This patient was scored Fazekas Grade 0. **(B)** Shows areas of hyperintensity in the periventricular regions (red arrow) and in the deep white matter (green arrow). This signature has been identified as a marker for leucoaraiosis. This image was blindly scored and on neuro-radiology report identified as Fazekas Grade 2.

TABLE 3 | Distribution of demographic, diathesis, stressor, and delirium severity indicators across delirium groups.

	No delirium ($n = 6$)	Subthreshold delirium ($n = 3$)	Full delirium ($n = 3$)	F Statistic
DEMOGRAPHICS				
Age	63.5 (12.2)	64.3 (9.5)	56 (9.6)	0.6
Education	12.5 (2.3)	13.3 (2.1)	13.3 (2.3)	0.2
% female	16.7%	66.7%	66.7%	NS
POTENTIAL DIATHESIS FACTORS (EXCLUDING VOXEL COUNT)				
Pre-operative CO_2 delta	4.8 (0.9)	4.6 (1.1)	5.1 (1.0)	0.2
Depressive symptoms (PHQ-9 Sum)	0.8 (1.0)	5.3 (4.0)	7.0 (4.6)	5.1*
Anxiety symptoms (GAD-7 Sum)	0.7 (0.5)	7.0 (8.7)	9.7 (7.0)	3.4
% illicit drug use past 2 weeks	0%	0%	33.3%	NS
NEUROPSYCHOLOGICAL FACTORS (PERCENTILES)				
Semantic fluency (Animals)	71.3	62.3	15.7	9.4**
Processing/executive functioning (DKEFS color word interference condition 1)	50.2	54.0	9.0	6.1*
Processing/executive functioning (DKEFS color word interference condition 2)	55.0	43.7	31.7	1.1
Spatial skills (CLOX 1)	82.8	47.0	56.5	18.9**
POTENTIAL STRESSOR FACTORS				
Length of Surgery	216.0 (123.8)	228.0 (192.3)	225.3 (138.1)	0.0
Intra-operative CO_2 Delta	12.1 (3.9)	14.5 (5.2)	12.3 (2.8)	0.4
Cerebral SAT (0 or 1)	0%	0%	66.7%*	$p = 0.03$*
Mean MAC	0.95 (0.13)	0.90 (0.0)	0.77 (0.29)	1.0
Intra-operative morphine equivalence (mg)	24.6 (17.3)	17.3 (11.2)	17.0 (7.2)	0.4
Total post-operative morphine equivalence (mg)	43.0 (28.0)	100.6 (99.1)	135.2 (78.0)	2.4
DELIRIUM FACTORS				
Average severity	1.9 (1.4)	3.5 (1.1)	6.9 (2.9)	7.9**
Peak post-operative severity	2.5 (1.1)	5.5 (0.5)	11.9 (3.4)	27.7***
Days in Hospital	3.0 (1.8)	4.7 (1.5)	5.7 (0.6)	3.3

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Analyses of variance were conducted for continuous variable and chi-square for categorical variables where percentages are reported and significance if applicable. For neuropsychological factors, F statistic and p-value based on scaled score for DKEFS condition 1 and 2, and Standard Score for Animals and CLOX 1. Percentiles reported for interpretability. NS, non-significant; PHQ-9, Patient Health Questionnaire – 9 item; GAD-7, Generalized Anxiety Disorder Scale – 7 item; DKEFS, Delis-Kaplan Executive Functioning System.*

occasional age-related lapses in short-term memory that was not noticed by loved ones. In the ST-POD group, 1 participant reported no change in cognition, and two indicated marked changes in cognition since surgery, providing examples such as "when picking up groceries I would forget what store I was in," "I tell the same story over and over." Of the full POD group, two participants described significant changes in memory and one did not. One POD patient reported that their spouse noticed significant cognitive changes and provided examples such as the more minor incident of "forgetting appointments," to the more extreme of "forgetting I am taking care of a newborn." The other POD patient was nonsensical, and had significant difficulty responding to any direct questions. This participant was able to indicate that they did not recall being home post-discharge for the first number of days. This person was assessed 4.5 months post-surgery.

DISCUSSION

The spectrum of acute confusional states following surgery, most commonly referred to as POD on the severe end of the spectrum, remains a perplexing and serious problem. Its management and consequences are time consuming, prolong hospital stay and have serious effects on long-term patient well-being (Vasunilashorn et al., 2016). A means to accurately predict those patients at risk would hopefully guide intra-operative and post-operative management and permit formal studies to more accurately address the problem. To the best of our knowledge, this study represents the most comprehensive, multidisciplinary approach to identify biomarkers of POD to date. We have assessed patients with a detailed neuropsychological battery prior to surgery, evaluated pre-operative psychiatric history, documented risk of intra-operative steal of cerebral blood flow for brain regions at risk by advanced neuroimaging techniques (MRI BOLD and axial FLAIR imaging) and tracked hemodynamics, end-tidal gases and cerebral oximetry in high fidelity intra-operatively to look for risk factors of POD. We also include a comprehensive POD assessment method, which derives severity scores and the ability to identify subthreshold manifestations, and longitudinally followed up with all participants.

We report on 12 adult patients receiving major surgery at a single site. As such this report represents a pilot study to inform the development of a stress-diathesis metric

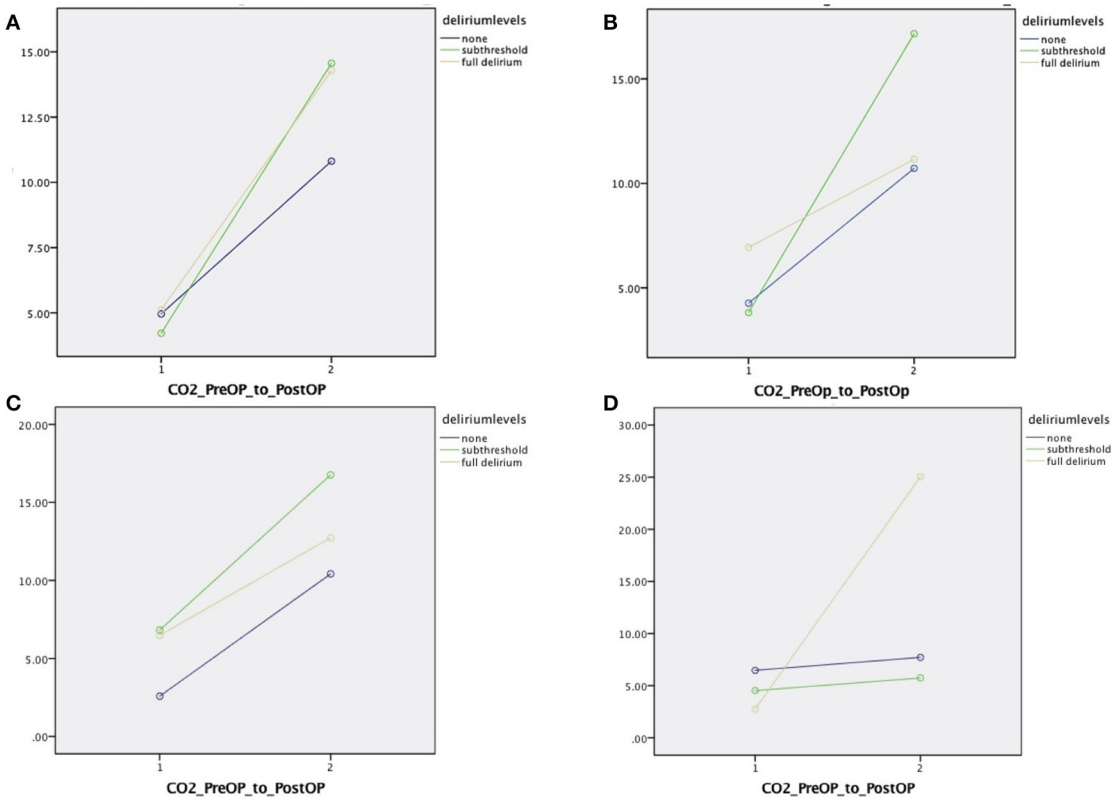

FIGURE 4 | (A) Repeated measures mixed effect analysis of variance examining change score in CO_2 delta pre- and post-measurement across POD levels adjusting for sex, education, and age. **(B)** Controls for semantic fluency scaled score, processing speed scaled score (DKEFS color word interference condition 1 and 2 scaled score mean), and history of psychiatric illness. **(C)** Controls for sociodemographics and Type 1 and 2 hypercapnic responses from white and gray matter. **(D)** Controls for sociodemographics and duration of surgery, cerebral SAT < 60, and mean MAC.

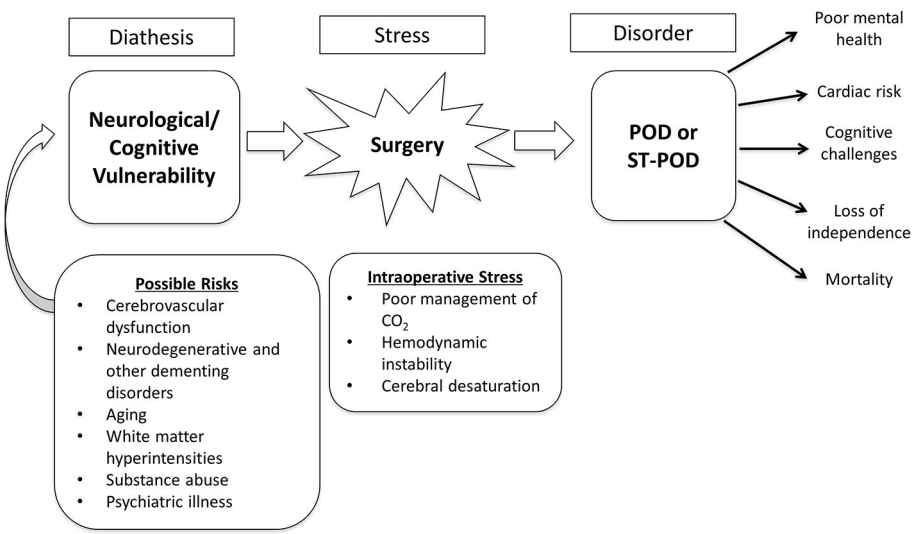

FIGURE 5 | Diagrammatic depiction of the stress-diathesis model for POD and ST-POD. See text for further details.

delineating risk of POD. We suggest that identifying psychiatric, neuropsychological (cognitive), and neurophysiological risk factors using symptom measures along with a pre-operative brain MRI CO_2 stress test and other advanced neuroimaging approaches, combined with assessment of intra-operative events, namely deviations in the conduct of anesthesia, can be predictive of ST-POD and POD. Based on the observations from this study, we also advance the idea that adherence to a brain protective protocol whereby normocapnia is maintained (or more precisely prevention of significant alterations in intra-operative CO_2 delta) may help decrease the incidence of POD and ST-POD in this patient population.

Diathesis Findings

The MRI BOLD CO_2 stress test (i.e., pre-operative exposure to graded CO_2 while undergoing neuroimaging) was employed as a separate indicator of risk in our stress-diathesis model to be used as a proxy for intra-operative stress. This procedure specifically involves a fixed vasodilatory stimulus that was administered to all patients—a CO_2 delta targeted to 5 mmHg during normoxic isoxia. This test has been successfully used to assess risk in other clinical scenarios. Risk stratification has been identified in patients with severe cerebrovascular compromise such as moya-moya disease, atherosclerotic stenosis or occlusion and more recently for concussion, white matter changes (leucoaraiosis) and dementia (Mandell et al., 2008; Fierstra et al., 2011; Han et al., 2011; Gao et al., 2013; Mutch et al., 2014, 2015; Sam et al., 2016a,b). All of these conditions have demonstrations of altered cerebrovascular reactivity, which become unmasked by controlled administration of CO_2 as a potent vasodilatory stimulus. In the present study, differences in response to CO_2 are evident between the patients without POD vs. those that manifested either full or ST-POD, with the most robust findings for full POD (see **Figures 1**, **2**). What is evident from the small case series here is that POD patients have a decreased response to the hypercapnic signal in gray and white matter (**Figure 1B**) and a trend to greater inverse response or intracranial steal (**Figures 1B**, **2B**). These findings have also been identified with a group of patients demonstrating leucoaraiosis (Pantoni, 2008; **Figure 3**). Quantification of these risks and their distribution requires an atlas of age matched surgical patients without POD to determine voxel thresholds for risk of POD. In this manner voxel count "cut points" can be determined. What is further evident from examination of these images is that there are various subgroups that help to define risk of POD. There is a group with essentially normal response to hypercapnia—both in gray and white matter—who did not demonstrate POD irrespective of the anesthetic course. Based on this finding there appears to be an identifiable low risk group defined by the CO_2 stress test. Another subgroup had an attenuated response to the hypercapnic stimulus and a greater signature for intracranial steal (both markers of cerebral dysregulation). This group is identified as high risk for POD. Whether or not these individuals manifested POD appeared to depend on both other pre-operative risk factors (e.g., neuropsychological functioning and psychiatric history) and their management during the anesthetic course (see **Tables 1, 2**, and further discussion below). A third subgroup had smaller signatures for CO_2 responsiveness and had a mixed response as to POD presentation. Importantly, in all patients the CO_2 delta was greater than a CO_2 delta targeted to 5 mmHg (during the CO_2 stress test) during the intra-operative course as shown in **Supplemental Table 1**. This suggests that our CO_2 stress test was very conservative to unmask risks of intracranial steal. Despite this, this change in CO_2 delta from the pre-operative stress test to the intra-operative period helped consolidate the stress-diathesis framework. As evident in **Figure 4**, including diathesis-related covariates (i.e., a) implicated neuropsychological vulnerabilities and presence of a clinically significant psychiatric profile, and b) intracranial steal responses during CO_2 stress test) greatly affect the full POD group, while including intra-operative stress covariates (i.e., duration of surgery, cerebral SAT < 60, and mean MAC) greatly affect the ST-POD group. This may suggest that intra-operative stress may play a larger role in ST-POD patients, a group with less pre-operative diathesis risk. With a larger sample size, rigorous prediction models will allow for a greater understanding of the diathesis and stressor contributions in POD.

With respect to pre-operative neuropsychological risk factors, preliminary data revealed that cognitive measures of semantic categorical fluency and information processing and speed/executive functioning were strongly associated with POD severity. This may correspond with vulnerabilities in temporal and frontal regions of the brain. Interestingly, POD severity was unrelated to measures of pre-operative phonemic fluency (F-A-S) despite the strong effect on semantic fluency; this discrepancy has been well documented as an indicator of Alzheimer's disease (Henry et al., 2004), which may represent an underlying contributor to POD. Relatedly, prior research has found that delirium accelerates cognitive decline in Alzheimer's disease, which may suggest related pathophysiology (Fong et al., 2009). The findings specific to these measures, which may reflect particular regional deficiencies, emphasizes the importance of examining a wide range of measures assessing specific cognitive abilities. Establishing an atlas of POD-free subjects could aid in determining if the MRI BOLD CO_2 stress test can be declarative in modeling these neuropsychological deficits based on attenuated response to the hypercapnic stimulus or an intracranial steal signature. This is important in order to use neuropsychological measures as a proxy for at-risk patients, as the administration of a pre-operative MRI BOLD CO_2 stress test is not feasible in general practice. The MMSE, which is the most widely used assessment tool in POD research, did not differentiate POD groups, nor was it associated with POD severity. Finally, as indicated in prior research, psychiatric illness emerged as being associated with POD, namely depressive symptoms. The emerging diathesis profile is similar to deficits reported in white matter hyperintensities and subcortical vascular dementia such as leukoaraiosis, characterized by depressive symptoms, motor and gait disturbances and cognitive deficits. In further support, in healthy older adults, white matter integrity is correlated with greater processing speed (Kerchner et al., 2012), which may suggest that the deficiencies in processing speed measures (DKEFS) is associated with reduced white matter integrity, which was correlated with POD.

Stressor Findings

The stressor was defined as the intra-operative anesthetic course. High fidelity hemodynamic and end-tidal gas output and continuous bifrontal cerebral saturation by cerebral oximetry were obtained using an intra-operative data acquisition system that downloaded the data stream at 0.5 hz (TrendFace Solo). These data were then binned to a minute-by-minute frequency. The data that were included to define the intra-operative stress and binarized were hypotension (mean blood pressure < 60 mmHg for a minimum of 1 min), elevated CO_2 delta $>$ 10 mmHg, duration of surgery greater than 120 min, and cerebral saturation <60% for greater than 1 min).

Although preliminary, our data demonstrate that inducing stress via CO_2 exposure pre-operatively allows for an index of brain response intra-operatively. Those demonstrating diathesis risk through specific cognitive vulnerabilities described above, psychiatric illness, and abnormal response to CO_2 stress are at highest risk of POD. As previously indicated, although several diathesis risk factors are linearly related to the severity of POD, it is hypothesized that the intra-operative anesthetic course will not demonstrate a clear linear relationship with outcomes, and may be more interactive.

The development of this stress-diathesis hypothesis, exhibited in **Figure 5**, is based on the current findings in combination with a number of recent findings that both emphasize the multifactorial nature of POD, the null findings with respect to anesthetic toxicity, studies demonstrating pre-existing structural and functional abnormalities in those with POD (Soiza et al., 2008), and the recent findings demonstrating the importance of pre-operative cognitive dysfunction in POD. One recent study examining pre-operative arterial spin labeling MRI using whole brain and globally normalized voxel wide analysis found that greater performance on neuropsychological measures correlated with cerebral blood flow, but these neuroimaging findings were not predictive of the risk of POD (Hshieh et al., 2016). Importantly, however, their study did not incorporate an assessment of intra-operative stress-related factors that would impact brain pathophysiology, which in isolation limits our understanding, as we believe it is the interaction between these brain vulnerabilities and the stress response (the stress-diathesis) that is predictive of both POD and ST-POD. Future research should aim to examine the relationship between cognitive deficiencies, and CO_2 stress test using BOLD MRI in order to understand whether these aforementioned correlations extend to emergent intracranial steal that may be anatomically indicated in part by leucoaraiosis or associated with alterations in cerebrovascular responsiveness in dementias—specifically as noted with Alzheimer's Disease.

Our findings are revealing and provocative. We acknowledge the small sample size of our study as a primary limitation. Despite this, we have identified biomarkers in neuropsychological testing and the psychiatric realm and MRI BOLD CO_2 stress test that when combined together may be predictive of POD. In addition, our sample size ($n = 12$) has been deemed large enough to adequately power fMRI studies for lower percent changes in activation of BOLD signal (Desmond and Glover, 2002). We have provided preliminary support for a stress-diathesis model based on these interactions and observations. Another limitation relates to defining features of subthreshold and full POD. We chose to use a newly validated POD severity measure to establish severity scores but acknowledge this may not fully encompass other potential markers such as the full spectrum of post-operative confusional states or low-grade encephalopathic states. However, our long-term follow-up provided clinical validity to these severity groups. Specifically, two-thirds of ST-POD or POD patients reported significant changes in cognition since surgery, with one who may have continued to meet criteria for POD over 4 months post-operatively. In comparison, 5/6 non-POD participants reported no change in memory following surgery, with one indicating potential mild age-related changes, which had not been corroborated by a loved one. Nonetheless, there are a number of etiological mechanisms that may manifest differently in acute confusional states in other contexts that warrants further exploration.

Clinical Implications

As previously indicated, neuroprotection of POD through anesthetic agents has not been supported. However, other means are available to provide neuroprotection to patients undergoing anesthesia for surgery in the operating room. Neuroanesthesia principles are time-honored and designed to optimize the surgical approach to the brain. It would seem to make sense to apply such approaches to the management of patients at risk for POD. While mild hypocapnia is usually maintained in neurosurgical procedures to reduce brain bulk, our findings here suggest that maintenance of normocapnia minimizing CO_2 delta intra-operatively may be the best course to choose for patients at risk of POD. There are older animal studies to support this contention. In two studies done using a paraplegia model, spinal cord was examined as a focus of injury. In these studies clear end-points of damage and comprehensive hemodynamics and end-tidal gases were reported. The first paper shows no difference between intravenous anesthesia (methohexital) or volatile agent (isoflurane) on the incidence of paraplegia suggesting the anesthetic agent is not at issue (Mutch et al., 1993b). The second paper shows a clear advantage of a neuroanesthesia approach (Mutch et al., 1993a).

An anesthetic approach tailored to rigorous control of intra-operative CO_2 may be appropriate as we now have greater understanding of the impact of alterations on CBF with changing levels of CO_2. When the brain manifests with cerebrovascular dysregulation, conditions exist for intracranial steal with elevation of CO_2 and the possibility of augmented flow to these areas with mild hypocapnia—the so-called "Robin Hood" effect. However, this effect is lost with subsequent elevation of the CO_2 tension leading to steal with return to normocapnia. This study has revealed the magnitude of change in CO_2 that can occur with major surgery. The mean delta was 13.2 ± 2.9 mmHg; range 7.5 – 20.0 mmHg. Thus, none of the patients had a CO_2 delta as low as the hypercapnic stimulus in the brain MRI CO_2 stress test. For this reason the voxel counts reported are conservative estimates of the response to CO_2 in any given patient. The effect of CO_2 intraoperatvely could be further confounding as all patients

received volatile agents—known cerebrovascular vasodilators. Patients are also at ischemic risk with hypotension and in this context the combination of hypotension with larger CO_2 deltas would be anticipated to be even more deleterious. An operative procedure where such a situation can routinely arise is with open aortic aneurysmectomy. With cross-clamp release hypotension in combination with large swings in CO_2 ensues. It has been noted that this patient group suffers with a very high incidence of POD (Salata et al., 2012). Especially important in the context of the MRI BOLD CO_2 stress test is delineating the magnitude of intracranial steal in brain at risk. Follow up studies where the brain stress test utilizes a greater CO_2 delta are being entertained; most likely using a ramp protocol of incremental CO_2 change that is better tolerated by patients, but able to examine a greater range (Fierstra et al., 2013; Sobczyk et al., 2014; **Supplemental Video 1**).

Importantly, maintenance of normocapnia as a prevention effort may also extend to intensive care settings, where POD rates are also high. Many of these patients will have the same diatheses, even the same stress if managed in a surgical ICU, following their operative intervention. Irrespective of management in a medical or surgical ICU, mechanical ventilation is extremely common, with swings in end-tidal CO_2 evident, often with hemodynamic instability. In fact, in intensive care units POD has been found to be associated with longer durations of mechanical ventilation (van den Boogaard et al., 2012), supporting this contention.

CONCLUSION

This study calls into question current conceptualizations of ST-POD and POD, significant and deleterious neuropsychiatric syndromes. Focus, to date, has been on modifying or limiting exposure to anesthetic agents. Our study suggests that an uncontrolled stress-diathesis may be driving high rates of ST-POD and POD. Specifically, preliminary data suggest that diatheses may be present that put particular patients at risk, particularly depressive symptoms, impaired semantic fluency and processing speed/executive functioning, and pathophysiological vulnerabilities that are evident on neuroimaging during exposure to controlled CO_2 prior to surgery. The latter represents a proxy for the proposed intra-operative stressor—fluctuations in end-tidal CO_2 during surgery, which may act as a catalyst for the expression of the spectrum of acute confusional states. We propose that the stressor itself could be mitigated by tight control of CO_2 in the normocapnic range acting as "neuroprotection" for those deemed at risk. A version of the stress-diathesis risk assessment as described here with comprehensive neuropsychological testing provides the testing platform for future investigations (Enzinger et al., 2007).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Biomedical Research Ethics Board (BREB) of the University of Manitoba with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Biomedical Research Ethics Board (BREB) of the University of Manitoba.

AUTHOR CONTRIBUTIONS

RE and WM contributed equally to this work including idea development, study design, methodology, personnel management, statistical analyses, and co-wrote the primary draft of the manuscript. RP contributed to design, methodology, personnel management, and reviewed drafts of the manuscript. KK contributed to methodology, participant recruitment, assessment, data collection and entry, and reviewed drafts of the manuscript. CB contributed to methodology, participant recruitment, assessment, data collection and entry, and reviewed drafts of the manuscript. CH contributed to methodology, participant recruitment, assessment, data collection and entry. LR contributed to MRI data collection, SPM processing and analysis. DF contributed to data collection and interpretation, and coordinated intra-operative management. RL contributed to data collection, entry, and management. JF, JD and DM contributed to idea development, study design, methodology, and interpretation of findings.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00274/full#supplementary-material

Supplemental Figure 1 | Explanation for intracranial steal demonstrated with the BOLD MRI CO_2 stress test as described in this study. **(A)** The CO_2 stress administered is shown at the bottom of the panel. This was an 11-minute stimulus (660 s). A block design triple hypercapnic stimulus each of 2 min at 5 mm Hg increase in CO_2 was interspersed with baseline end-tidal CO_2. Importantly the end-tidal O_2 was "clamped" at approximately 110 mmHg during the changes in CO_2 (this response is not shown). In the middle row the BOLD response at one voxel is shown for the anticipated response BOLD signal increase with hypercapnia—an increase in cerebral blood flow (CBF) compared with baseline CO_2 is shown for the triple stimulus (highlighted in gray). The red dots depict a single scan BOLD signal response (330 dots or one scan every 2 s). The tight response to the triple stimulus is shown in the left panel. The inverse response in one voxel is shown in the right panel –greater BOLD signal at baseline CO_2 and BOLD signal decreasing with hypercapnia—a paradoxical response as CBF has

decreased with increasing CO_2—an example of intracranial steal in this voxel. The top panel shows the distribution of voxels for the two responses (so-called "glass brain" depiction). A voxel is gray—increasing hue as the *t*-value statistic increases above the cut point at the chose *p*-value ($p = 0.001$ in this circumstance). Most voxels demonstrate the expected behavior to the stimulus. The right top panel shows those voxels—far fewer in number - that demonstrate the inverse response or intracranial steal. **(B)** The glass brain statistical distribution of voxels is now colorized in the left panel. Increasingly hot colored (orange hues) voxels show where CBF has increased in response to the CO_2 stimulus. The cold-colored (blue hue) voxels show regions of intracranial steal. These are largely in periventricular or deep white matter regions (fuller explanation in the text). A parallel flow model showing contiguous regions explaining intracranial steal and normal response is shown in the right panels. With flow-limited input (the CBF response is flow limited and demonstrates a sigmoid response to increasing CO_2) normally flow increases regionally with increasing CO_2 and the BOLD signal increases – shown as increasing orange hues in the micro-regional (green circle) distribution. In diseased areas with abnormal response (vasoparalysis) flow can be stolen from this region as the vasculature is already maximally vasodilated and thus paradoxically "feeds" the normal vasodilating adjacent region. This is depicted as increasing bluish hue in the green vascular circle. The green circle shows such a region in the colorized image with a blue steal region next to a normal orange region. The parallel path for the two regions is shown to the right with normal vasomotion shown as an arrow directed outward from the feeding vessel and abnormal vasomotion shown as a double headed arrow with paralyzed effectiveness. The normal response is highlighted by the green circle in the lower figure (showing hot coloration throughout and increasing orange hue depicting increased CBF). The parallel distribution is shown in the bottom right panel. Normal vasomotion occurs in both parallel arms in the depiction to the right of this region.

Supplemental Video 1 | This video depicts the dynamic response of the human brain to alterations in end-tidal CO_2 tension. The left panel shows the CO_2 stimulus over time. The CO_2 delta here is approximately 20 mmHg—the upper limit of change in CO_2 seen in this study. The right panel shows the changes in BOLD CVR to the CO_2 stimulus. The signal changes to an essentially cold response (blue voxels) indicating decreased BOLD response with hypocapnia (an index of decrease cerebral blood flow (CBF) with a decrease in CO_2). As the CO_2 increases, increasing above the baseline value the brain response gets hotter (shades of orange). This correlates with an increase in CBF with the increase in CO_2. A return toward baseline values occurs as the CO_2 stimulus abruptly returns to the starting value. This ramp sequence indicates a more reflective CO_2 delta for the intra-operative stress observed.

Supplemental Table 1 | The end-tidal gases for each subject are shown—baseline CO_2 (CO_2 BL), CO_2 delta, and mean O_2 in mm Hg. A comparison between the non-POD and combined ST-POD- and POD-values and *t*-statistics are also shown.

Supplemental Data Sheet 1 | A glossary of anesthesia terms relating to gas exchange and intracranial steal.

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frontiers in Aging Neuroscience

HYPOTHESIS AND THEORY
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Remote Ischemic Conditioning: A Novel Non-Invasive Approach to Prevent Post-Stroke Depression

*Wenbo Zhao[1], Fang Jiang[1], Zhen Zhang[1], Jing Zhang[1], Yuchuan Ding[2] and Xunming Ji[3]**

[1]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China, [2]Department of Neurosurgery, Wayne State University School of Medicine, Detroit, MI, United States, [3]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China

Post-stroke depression (PSD) is a common neuropsychiatric complication of stroke. However, due to the high expense and side effects of pharmacotherapy and the difficult-to-achieve of psychotherapy, the prevention and treatment of PSD are still far from satisfaction. Inflammation hypothesis is now playing an essential role in the pathophysiological mechanism of PSD, and it may be a new preventive and therapeutic target. Remote ischemic conditioning (RIC) is a non-invasive and easy-to-use physical strategy, which has been used to protect brain (including ischemic and hemorrhagic stroke), heart and many other organs in clinical trials. The underlying mechanisms of RIC include anti-inflammation, anti-oxidative stress, immune system regulation and other potential pathways. Our hypothesis is that RIC is a novel approach to prevent PSD. The important implications of this hypothesis are that: (1) RIC could be widely used in clinical practice to prevent PSD if our hypothesis were verified; and (2) RIC would be thoroughly explored to test its effects on other neurobehavioral disorders (e.g., cognitive impairment).

Keywords: remote ischemic conditioning, post-stroke depression, stroke, neuropsychiatric complication, depression and anxiety disorders

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Lia Fernandes,
University of Porto, Portugal

Reviewed by:
Wei Wang,
Stowers Institute for Medical Research, United States
Renerio Fraguas,
University of São Paulo, Brazil

****Correspondence:***
Xunming Ji
jixm@ccmu.edu.cn

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INTRODUCTION

Post-stroke depression (PSD) is one of the most frequent and important neuropsychiatric complications of stroke. One third of stroke survivors experienced major depression, and what's worse, the prevalence of minor and moderate depression is much higher (Robinson and Jorge, 2016). Studies showed that PSD has adverse effects on functional recovery, cognitive function and social and interpersonal activities, and it can also increase mortality (10 times higher than in patients without PSD; Espárrago Llorca et al., 2015).

In clinical practice, however, PSD is generally undiagnosed and undertreated. Thus the prevention of PSD may be more important than its treatment in the real world. Psychotherapy and antidepressants (e.g., Escitalopram) may be effective in preventing the occurrence of PSD (Robinson et al., 2008; Nabavi et al., 2014). However, due to the high expense and side effects of pharmacotherapy and the difficult-to-achieve of psychotherapy, rigorous clinical trials are needed to determine their utility after acute stroke (Mohr et al., 2006; Peterson et al., 2017). Currently, the mechanisms of frequently-used antidepressants are largely based on the monoamine hypothesis, and all these pathways have anti-inflammatory effects directly or indirectly (Dwyer Hollender, 2014). Furthermore, inflammation hypothesis has been an important pathophysiological mechanism of depression (Kohler et al., 2016). Therefore, anti-inflammation may be a new target for the prevention and treatment of PSD.

Remote ischemic conditioning (RIC) is a protective systemic strategy by which one or more cycles of brief, nonlethal limb ischemia confer protection to distant organs (Meng et al., 2012; Hausenloy et al., 2015; Meybohm et al., 2015). It has been proven to be an effective strategy for cardioprotection in patients with ischemic cardiovascular diseases, and it is also effective for neuroprotection in patients with hemorrhagic stroke, acute ischemic stroke and chronic cerebral ischemia (Meng et al., 2012; Hougaard et al., 2014; Hausenloy and Yellon, 2016; Laiwalla et al., 2016; Zhao et al., 2017). The underlying mechanisms involved in providing RIC induced distant organs protection include anti-inflammation, anti-oxidative stress, immune system regulation, autonomous nervous system regulation and other potential pathways (Randhawa et al., 2015). Against these backgrounds, we assume that RIC may inhibit several pathways of PSD and have beneficial effects on the prevention of PSD.

THEORY OF THE HYPOTHESIS

Our hypothesis is that RIC is a novel approach to prevent PSD. Currently, RIC has been widely used in clinical trial to test its effects on organic diseases of heart, brain, kidney, limb and other organs. It has been shown to inhibit recurrent stroke effectively in patients with ischemic stroke (Meng et al., 2012, 2015), reduce the incidence of new brain lesion on MRI after carotid artery stenting (Zhao et al., 2017), and improve functional outcomes in patients with hemorrhagic stroke (Laiwalla et al., 2016). However, no study focuses on RIC's effects on psychological dysfunction.

Recently, several studies have provided support for the role of inflammatory response in the development of PSD, which has been further supported by clinical findings of increased serum inflammatory cytokines in patients who developed PSD (Spalletta et al., 2006, 2013; Li et al., 2014). Furthermore, inflammation has complex interactions with monoamine system, hypothalamic-pituitary-adrenal (HPA) axis and neuroplasticity, and all of them contribute to the pathophysiological mechanisms of PSD (Fang and Cheng, 2009; Li et al., 2014).

The mechanisms involved in providing RIC induced organs protection are quite complex and interlinked, but its effects on inflammation may be one of the most important ones (Hausenloy and Yellon, 2008; Randhawa et al., 2015). Clinical researches showed that RIC could reduce plasma inflammatory markers (e.g., high sensitive C-reactive protein, interleukin-6) in stroke patients (Meng et al., 2015). In addition, RIC has many other potential pathways to induce organ protection (Randhawa et al., 2015), and some of them may also exist in the underlying mechanism of PSD (**Figure 1**).

EVALUATION OF THE HYPOTHESIS

Our hypothesis could be supported by the evidences that the mechanism of RIC includes anti-inflammation, immunoregulation, antioxidant and other underlying pathways, which are also existed in the pathophysiology of PSD.

Like many psychiatric disorders, however, psychological, social and biological factors all play their roles in the occurrence of PSD (De Ryck et al., 2014). Furthermore, PSD can be influenced by many other factors, including genetic factors,

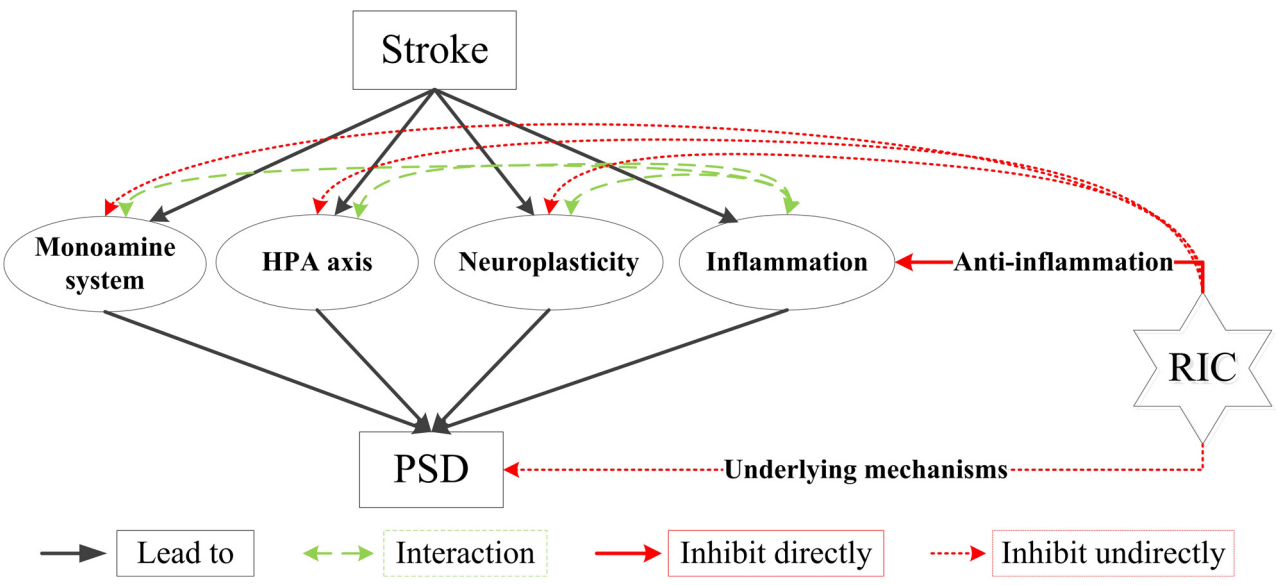

FIGURE 1 | Main biological mechanisms of PSD and how RIC plays its roles in preventing PSD. HPA indicates hypothalamic-pituitary-adrenal; PSD, post-stroke depression; RIC, remote ischemic conditioning. Stroke leads to PSD through several biological mechanisms, such as the ascending monoamine systems, the abnormality of HPA axis, the alteration of neuroplasticity and inflammation. Inflammation also has complex interactions with monoamine systems, HPA axis and neuroplasticity. RIC can prevent PSD through anti-inflammation and other underlying mechanisms directly, and it has effects on monoamine systems, HPA axis and neuroplasticity indirectly. All these effects of RIC could be the potential pathways to prevent and treat PSD.

medical and psychiatric history, stroke characteristics and lesion location, and social support. Therefore, the effect of RIC on PSD might be limited in some kinds of patients, and selecting the potentially benefited populations may be a key issue. Therefore, ischemic stroke patients with left hemisphere infarction, greater severity and less social support might be better choice for clinical trials that determining the efficacy of RIC for PSD.

We plan to test our hypothesis by both animal experiment and clinical trial:

1. **Animal experiment**: stroke model will be induced by occluding the middle cerebral artery using the intraluminal filament technique, and then chronic mild stress will be applied to the model to induce depression (Willner et al., 1987). RIC will be applied to part of the stroke model. RIC will be initiated following the stroke by bilaterally occluding blood flow to the hind limbs with method used by Ren et al. (2015). The incidence of PSD and the concentration of monoamine neurotransmitter in brain tissue will be recorded to measure the results.
2. **Clinical trial**: we will recruit ischemic stroke patients and apply RIC to them by the method used by Meng et al. (2012), and RIC will be performed twice daily for 6 months. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) will be used to determine depression, Hamilton Depression Rating Scale (HAMD) will be used to evaluate the severity of depression, and plasma biomarkers (including interleukin 1, interleukin 6 and interleukin 10) will be tested to determine the underlying mechanisms. The primary outcome is the incidence of PSD within 6 months after stroke onset. The secondary outcomes include: (1) recovery of neurological dysfunction; (2) change in plasma biomarkers; (3) recurrent of ischemic cerebrovascular events; and (4) any adverse events.

IMPORTANT IMPLICATIONS OF THE HYPOTHESIS

If this hypothesis were verified by animal and clinical studies, RIC could be widely used in clinical practice to prevent PSD and thoroughly explored to test its effects on other neurobehavioral disorders (e.g., cognitive impairment). Compared with current strategies (i.e., psychotherapy and pharmacotherapy) for the treatment of PSD and other neurobehavioral disorders, the advantages of RIC include that: (1) it is a non-expensive and safe therapy, and no severe side effects has been reported; (2) it has multiple organs (e.g., brain, hear, kidney, liver, limbs, lung) protection, and multiple diseases preventions and treatment; (3) its usage can be learnt easily, and it is easily to be used, which even can be done with a sphygmomanometer; and (4) it can be done without the requirement of special place. Of course, RIC still has several limitations, which may limit its popularization. To date, we still do not know the exact mechanisms and the optimal protocol of RIC, and it may be time consume and cause skin petechiae. In addition, RIC cannot be performed on limbs with any vascular, soft tissue, or orthopedic injury (Zhao et al., 2017).

CONCLUSION

RIC might be a novel non-invasive and easy-to-use strategy for preventing PSD. Functional recovery of stroke survivors would be further improved and the mortality would be decreased significantly. If our hypothesis is confirmed by our animal experiment and clinical trial, RIC would be thoroughly explored in clinical trials to test its effects on psychological disorders and other post stroke neurobehavioral disorders (e.g., cognitive impairment).

AUTHOR CONTRIBUTIONS

WZ and FJ wrote the draft. WZ made the Figure. All authors contributed to the critical revision of the manuscript and have approved the final version of this review article.

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frontiers in Aging Neuroscience

ORIGINAL RESEARCH
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Enhanced Gamma Activity and Cross-Frequency Interaction of Resting-State Electroencephalographic Oscillations in Patients with Alzheimer's Disease

Jing Wang[1,2,3], *Yuxing Fang*[4], *Xiao Wang*[1,2,3], *Huichao Yang*[4,5], *Xin Yu*[1,2,3] *and Huali Wang*[1,2,3]*

[1]*Peking University Sixth Hospital (Institute of Mental Health), Beijing, China,* [2]*National Clinical Research Center for Mental Disorders, Key Laboratory of Mental Health, Ministry of Health, Peking University, Beijing, China,* [3]*Beijing Municipal Key Laboratory for Translational Research on Diagnosis and Treatment of Dementia, Beijing, China,* [4]*National Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China,* [5]*IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China*

Cognitive impairment, functional decline and behavioral symptoms that characterize Alzheimer's disease (AD) are associated with perturbations of the neuronal network. The typical electroencephalographic (EEG) features in AD patients are increased delta or theta rhythm and decreased alpha or beta rhythm activities. However, considering the role of cross-frequency couplings in cognition, the alternation of cross-frequency couplings in AD patients is still obscure. This study aims to explore the interaction dynamics between different EEG oscillations in AD patients. We recorded the resting eye-closed EEG signals in 8 AD patients and 12 healthy volunteers. By analyzing the wavelet power spectrum and bicoherence of EEG, we found enhanced gamma rhythm power in AD patients in addition to the increased delta and decreased alpha power. Furthermore, an enhancement of the cross-frequency coupling strength between the beta/gamma and low-frequency bands was observed in AD patients compared to healthy controls (HCs). We propose that the pathological increase of ongoing gamma-band power might result from the disruption of the GABAergic interneuron network in AD patients. Furthermore, the cross-frequency overcouplings, which reflect the enhanced synchronization, might indicate the attenuated complexity of the neuronal network, and AD patients have to use more neural resources to maintain the resting brain state. Overall, our findings provide new evidence of the disturbance of the brain oscillation network in AD and further deepen our understanding of the central mechanisms of AD.

Keywords: Alzheimer's disease, oscillations, resting-state, EEG, cross-frequency coupling

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Edited by:
Alessio Avenanti, Università di Bologna, Italy

Reviewed by:
Changsong Zhou, Hong Kong Baptist University, Hong Kong
Seung-Goo Kim, Max Planck Institute for Human Cognitive and Brain Sciences (MPG), Germany

***Correspondence:**
Huali Wang
huali_wang@bjmu.edu.cn

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive deficits, disorders of activities of daily living and behavioral disturbance, with widespread cortical atrophy mainly localized in the temporal-parietal lobe (Marceglia et al., 2016).

Electroencephalography (EEG) rhythmical oscillations in the low (delta, theta and alpha) and high (beta and gamma) frequencies have been demonstrated to be linked to a broad variety

of perceptual, sensorimotor and cognitive processes (Schroeder and Lakatos, 2009). Increasing evidence has shown that the resting state EEG rhythms may reveal abnormalities of the basic neurophysiological mechanisms that underlie vigilance and cognition in AD subjects. These abnormal EEG rhythms are thought to be associated with functional cortical disconnections, resulting in the death of cortical neurons, axonal pathology and neurotransmission deficits (Tsolaki et al., 2014).

Previous studies have shown that compared to normal elderly subjects, AD patients are characterized by high power of delta (<4 Hz) and/or theta (4–7 Hz) rhythms and low power of alpha (8–12 Hz) and/or beta (13–30 Hz) rhythms (Babiloni et al., 2016). In addition, other studies reported the increased delta coherence, decreased theta and alpha coherence, higher alpha and lower delta and beta small world characteristics of connectivity (Marceglia et al., 2016; Vecchio et al., 2017) in AD patients. Some reports (Tsolaki et al., 2014) also found the correlation between the degree of the EEG abnormality and the cognitive impairment in AD patients, including the correlation between EEG delta, theta, and alpha activities and Mini Mental Status Examination (MMSE) scores, between theta/gamma ratio and worse performance in nonverbal learning tests, between lagged phase synchronization in the theta band and MMSE scores.

However, the alteration of gamma band during resting state in AD patients is still obscure. Gamma rhythm has been verified to play an important functional role during cognitive functions (Missonnier et al., 2010). Some studies have showed disturbed task-induced gamma dynamics in AD patients and mouse models of AD, including increased auditory steady state gamma amplitudes (Osipova et al., 2006), delayed gamma responses, higher gamma fractal dimension values (Basar et al., 2016), increased high-frequency coherence (Hogan et al., 2003), and decreased high-frequency spectral powers in the frontal and temporal areas (Koberda et al., 2013; Stoiljkovic et al., 2016). Therefore, it is also interesting for exploration the abnormality of gamma rhythm in AD patients.

Furthermore, different EEG oscillations in the frequency domain are not independent; in contrast, the mutual interaction of cross-frequency oscillations regulate multi-network integration (Buzsáki and Watson, 2012). For example, the magnitude of theta-gamma coupling in the hippocampal region varied with working memory load (Axmacher et al., 2010). One recent study found that impaired theta-gamma phase-amplitude coupling was associated with the cognitive deficits in the mice of the AD model (Zhang et al., 2016). However, the abnormality of cross-frequency couplings in AD patients is still obscure, and it is also critical for understanding the underlying mechanisms of the multi-dimensional decline in AD patients.

Considering the role of brain oscillations and cross-frequency interactions in memory and cognition, in this study, we aimed to explore the interaction dynamics between different EEG oscillations, including the power information and cross-frequency coupling in AD patients compared with the healthy volunteers.

MATERIALS AND METHODS

Participants

This study was approved by the ethics committee of the Peking University Institute of Mental Health. Written informed consent was obtained from the participants and their families at the beginning of the study. No vulnerable populations were involved in this study. All subjects were Chinese Han, right-handed and more than 55 years old. Patients with AD were prospectively recruited from the Dementia Care and Research Center, Peking University Institute of Mental Health. A clinical diagnosis of AD was made according to the criteria for dementia cited in the International Classification of Diseases, 10th Revision (ICD-10; World Health Organization, 1999) and the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and the Stroke/AD and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). Other inclusion criteria were as follows: more than 6 months' duration of the disease and MMSE score of 15–24. Exclusion criteria comprised any type of evidence of other forms or causes of dementia, such as frontotemporal dementia, vascular dementia, Parkinson's disease, Lewy body dementia, metabolic syndrome, nutritional deficits and tumors. The healthy elderly subjects had no history of neurological or major psychiatric disorder. They underwent medical, neurological and psychiatric assessments, including MMSE and clinical dementia rating (CDR), to exclude actual neurocognitive disorders and major psychiatric symptoms (including abuse of substances). Finally, this study involved 8 patients with AD and 12 healthy elderly individuals, which were carefully matched for age, gender and years of education.

Neuropsychological Assessment

Each participant underwent a thorough neuropsychological assessment, including the MMSE, immediate and delayed memory test of Wechsler memory scale (WMS), Raven's combined progressive matrices (RCPM), Beck depression inventory (BDI-II), digit span test, and attentional matrices test. The function was assessed with the activities of daily living scale (ADL).

EEG Recording and Pre-Processing

We employed the 32-channel EEG system (bandpass: 0.01–100 Hz; Brain Products GmbH, Munich, Germany) for the collection of EEG signals. The 32 scalp electrodes were positioned over the whole head according to the 10–20 System, with the Cz electrode as the reference electrode. Electrode impedance was kept below 20 kΩ. All subjects were kindly asked to stay relaxed with their eyes closed and not to move or talk; then, 5 min of EEG signals were recorded.

Signals were analyzed offline with Matlab (The Mathworks, Natick, MA, USA) EEGLAB software. All recorded artifact-free EEG data were re-referenced off-line to a common average. The EEG signals were digitized at a sampling rate of 500 Hz, re-referenced to an average of residual channels, band-pass filtered in the range of 1–45 Hz to avoid the interference of

50 Hz signals and subsequently inspected for artifact rejection; conspicuous baseline drift and artifacts caused by eye movement were eliminated by visual inspection on time series, and the automatic artifact rejection threshold was set to ±100 μV.

Data Analysis

We used the wavelet power spectrum analysis method to obtain the power of the spontaneous EEG activities (Shaw et al., 1999). The Morlet wavelet transform was employed with the wavelet central angle frequency of 6 (ω = 6). The following five frequency bands were examined: 1–4, 4–8, 8–13, 13–30, 30–45 Hz, corresponding to delta, theta, alpha, beta and gamma bands, respectively (Mantini et al., 2007), with a step of 0.5 Hz.

Cross-frequency interaction often reflects the synchronization of networks, and the power spectrum could not include the phase information. To evaluate the degree of cross-frequency phase couplings, we measured the co-modulation of oscillations between two frequency bands with general harmonic wavelet bicoherence (Li et al., 2009). The bicoherence method is the normalized form of the bispectral analysis, which we described in our previous study (Li et al., 2009; Wang et al., 2013). Briefly, signals were divided into a series of 2-s epochs, with an overlap of 75%. Then, for each epoch, bicoherence values were computed in all pairs of frequencies from 1 Hz to 45 Hz, with a step of 1 Hz and a bandwidth of 2 Hz. Finally, the filtered wavelet bicoherence value (abbreviated as FIWBIC) was calculated using the same epoch as the power analysis above.

For the demographic information, an unpaired *t*-test was used to compare the difference between two groups.

TABLE 1 | Demographics and clinical characteristics of the participants.

	AD (*N* = 8)	HC (*N* = 12)	*P*
Gender (men/women)	4/4	7/5	0.7136
Age	76.88 ± 0.74	73.67 ± 2.30	0.2834
Years of education	13.13 ± 0.91	14.68 ± 0.67	0.2041
MMSE	22.5 ± 1.35	29.08 ± 0.29	<0.0001***
BDI-II	8 ± 1.78	4.92 ± 1.15	0.1445
WMS			
Immediate memory	2.75 ± 0.98	9.46 ± 0.74	<0.0001
Delayed memory	1.38 ± 1.02	12.73 ± 0.99	<0.0001
RCPM	25.88 ± 1.06	30.27 ± 1.83	0.0774
ADL	30.75 ± 3.36	20.36 ± 0.36	0.0021**
Digit span			
Forward	6.63 ± 0.32	7 ± 0.21	0.3292
Backward	3.25 ± 0.31	5 ± 0.50	0.0157*
Attentional matrices			
PC (%)	84.59 ± 2.40	94.09 ± 1.68	0.0038**
PE (%)	67.86 ± 6.74	88.16 ± 2.31	0.0052**

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

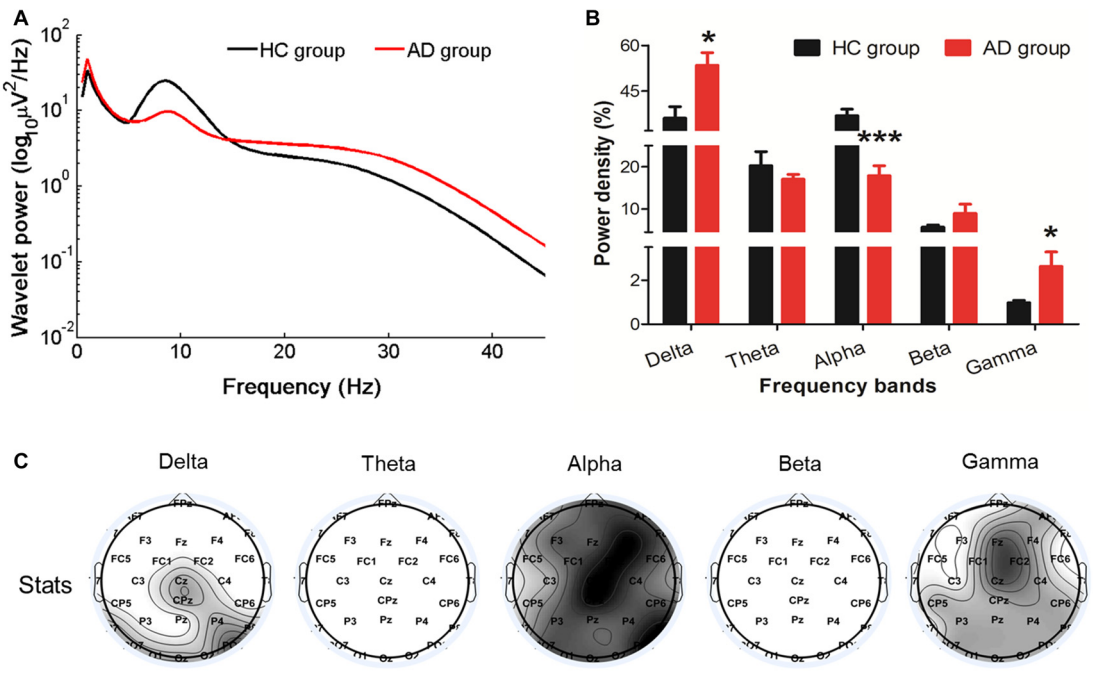

FIGURE 1 | Changes in the EEG power spectra in the Alzheimer's disease (AD) group compared with the healthy control (HC) group. **(A)** The average absolute EEG power in HCs (black line) and AD patients (red line). The *Y-axis* represented the power value and the *X-axis* represented frequency bands. **(B)** The relative power (normalized to the overall power) in five frequency bands. A marked increase of the relative power in delta and gamma frequencies and a decrease in alpha frequency was observed in the AD group (red columns) compared with the power in the HC group (black columns). *$P_{FDR} < 0.05$, ***$P_{FDR} < 0.001$ compared with the HC group. All data were expressed as the means ± SEM (n = 8–12). **(C)** Topographic distribution of statistical significances in EEG power in the AD group compared with the HC group. Values were color coded. Black: $P < 0.001$; dark gray: $P < 0.01$; light gray: $P < 0.05$; white: not significant, uncorrected for the number of electrodes tested.

For power spectral data, a nonparametric permutation test (Wang et al., 2015) was used to identify the difference in the frequency ranges of EEG power between the two groups (the number of permutations = 10,000, $P < 0.05$). The False Discovery Rate (FDR; Benjamini and Yekutieli, 2001) was conducted for multiple comparisons correction (the number of multiple comparisons = 5).

For the wavelet bicoherence data, we focused on the characteristics to determine the differences between two groups; prior to the contrast, the characteristic total bicoherence value at the frequency bands ($f_j^L \leq f_j \leq f_j^U$ and $f_k^L \leq f_k \leq f_k^U$) was extracted, which was defined as $b = \sum\sum b^2_{xxx}(f_j, f_k)$, where b_{xxx} is FIWBIC. This value reflects a measure of the degree of quadratic phase coupling (QPC) between frequency bands and can be used to measure the phase coupling strength between different oscillations (Li et al., 2009). Then, a nonparametric permutation test was employed to determine marked differences (the number of permutations = 10,000), with a P value less than 0.05 (FDR corrected, the number of multiple comparisons = 10) as a statistically significant standard.

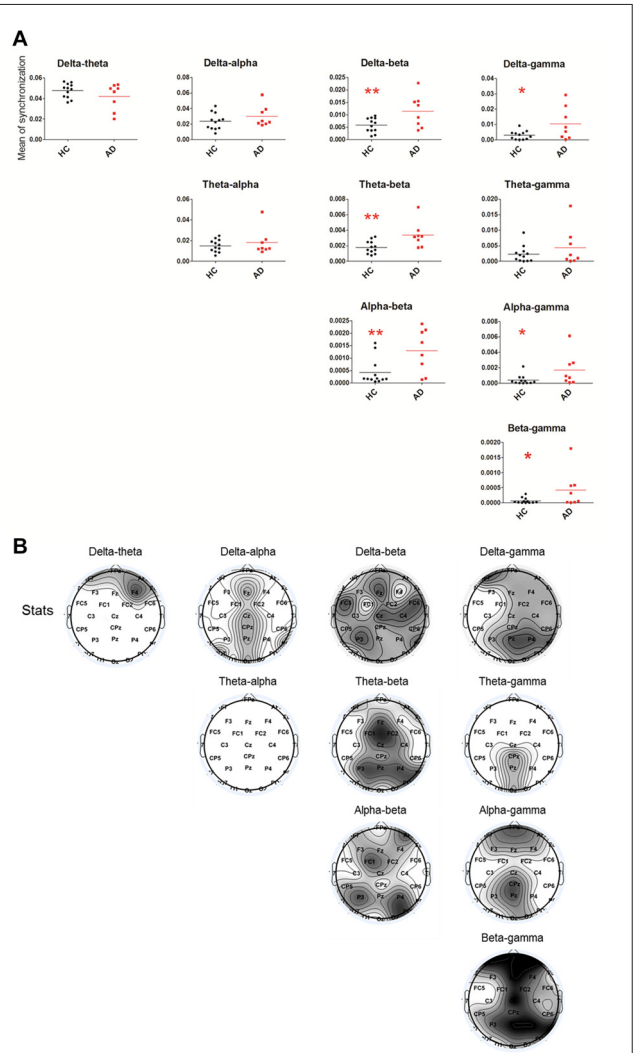

FIGURE 2 | Statistical analysis of filtered wavelet bicoherence value (FIWBIC) in the AD group compared with the HC group and topgraphic distribution of statistical differences. **(A)** Scatter plot for phase coupling at local frequency bands in the HC group (black) and AD group (red).The *Y-axis* represented the mean of synchronization. The synchronization values increased between between beta and delta/theta/alpha, and between gamma and delta/alpha/beta. $^*P_{FDR} < 0.05$, $^{**}P_{FDR} < 0.01$, (n = 8–12). **(B)** Topographic distribution of statistical significances in cross-frequency coupling between two groups. Values were color coded. Black: $P < 0.001$; dark gray: $P < 0.01$; light gray: $P < 0.05$; white: not significant, uncorrected for the number of electrodes tested.

RESULTS

There was no significant difference in age, gender, education level, intelligence and BDI-II score between the AD and healthy control (HC) groups. As expected, a remarkable difference was found for the MMSE score ($P < 0.0001$), activities of daily living ($P = 0.0021$), WMS immediate and delayed memory score ($P < 0.0001$), digit span backward score ($P = 0.0157$), percentage of correctness ($P = 0.0038$) and efficiency ($P = 0.0052$) for attentional matrices test in AD patients compared with the HC group (**Table 1**).

Compared with the HC, the relative resting-state wavelet power of delta ($P = 0.0149$) and gamma ($P = 0.0194$) frequency oscillations increased, and the power of alpha bands decreased ($P = 0.0003$) in the AD group (**Figures 1A,B**). Furthermore, we found that the increased delta was mainly located in the central-parietal and occipital areas, the decreased alpha was widespread around the entire cortical area, and the increased gamma was mainly located in the midline frontal, central-parietal and occipital areas (**Figure 1C**).

Relative to the HC group, the cross-frequency coupling strength between beta and delta ($P = 0.0098$), beta and theta ($P = 0.0035$), beta and alpha ($P = 0.0079$), gamma and delta ($P = 0.0184$), gamma and alpha ($P = 0.0079$) and gamma and beta ($P = 0.0162$) in the AD group (**Figure 2A**) was significantly increased, indicating stronger synchronization among the high-low frequency bands. Furthermore, we found that the increased delta-theta coupling was mainly located in prefrontal, the increased delta-beta coupling was widespread around the entire cortical area, the increased delta/beta and gamma couplings were located in cortical areas except for left temporal area, the theta-gamma coupling was increased in midline parietal-occipital area, whereas the increased theta/alpha-beta couplings and alpha-gamma coupling were located in cortical areas except for bilateral temporal lobes in AD group (**Figure 2B**).

However, we did not observe a significant relationship between the wavelet power, phase coupling strength with the neurocognitive performance ($P > 0.05$).

DISCUSSION

By analyzing the wavelet power spectrum and bicoherence of EEG, we found that, in AD patients, expected for the increased delta and decreased alpha power, the resting-state

gamma rhythm power was enhanced and was mainly located in the midline frontal, central-parietal and occipital areas. Furthermore, the enhancement of the cross-frequency coupling strength between beta and delta/theta/alpha, between gamma and delta/alpha/beta were observed in AD patients compared to HCs, and were also mainly located in the frontal, parietal-occipital areas.

In our study, compared to HCs, we found more pronounced delta power mainly located in the central-parietal and occipital areas and less prominent widespread alpha power in AD patients. In line with previous studies, these changes were recognized as typical EEG alterations in patients with dementia (Babiloni et al., 2010, 2013). Notably, alpha oscillations have been suggested to play an important role in cognitive and memory processing (Klimesch, 1999). Therefore, the increase of delta and weakened alpha rhythm in our study may reflect deficits in brain activity or cognitive decline (Hsiao et al., 2013).

Interestingly, we found AD patients showed higher power in resting-state high-frequency oscillation, especially in gamma band, which mainly located in the midline frontal, central-parietal and occipital areas. It was inconsistent with the findings in some report (Koberda et al., 2013; Stoiljkovic et al., 2016), in that article, decreased stimulation-elicited hippocampal gamma power was reported in mice of AD model. This divergence might be related to different states of EEG recording and the severity of the disease. Gamma rhythm has been indicated to play a relevant functional role during perceptual, executive and mnemonic processes (Missonnier et al., 2010). It arises from the inhibitory GABAergic parvalbumin-expressing (PV) interneurons network (Buzsáki and Wang, 2012). Many mouse models of AD have been generated with a growing realization that dysfunction of the GABAergic network plays a role in AD pathogenesis (Verret et al., 2012; Hazra et al., 2013; Ma and McLaurin, 2014). Therefore, it is reasonable that abnormal on-going gamma oscillation exists in AD patients.

In view of the relationship between gamma oscillation and neurotransmitters, the GABAergic interneurons receive excitatory inputs through N-methyl-D-aspartate (NMDA) receptors and are inhibited by the activation of metabotropic muscarinic receptors (mAChRs) on its terminal (Picciotto et al., 2012); therefore, dysfunction of acetylcholine (Ach) and NMDA neurotransmission may result in abnormalities of gamma oscillation. Memory and cognitive decline in aging and dementia are associated with synaptic/extrasynaptic NMDAR over-activation by glutamate and decreased cholinergic function. Additionally, Aβ deposition, which played an important role in pathophysiology of AD, interfered with NMDA neurotransmission and suppressed NMDAR-dependent synaptic functions (Cissé et al., 2011). Based on these data, it is conceivable that the enhanced power in gamma oscillations in our results might reflect the continuous gamma discharge resulting from the over-activation of the GABAergic interneuron network induced by extrasynaptic NMDAR over-activation and decreased cholinergic function in AD patients.

Considering the integration of cross-frequency interactions in different networks, we further found an increase in the cross-frequency coupling strength between the high-frequency bands (beta/gamma) and low-frequency bands (delta/theta/alpha), which were mainly located in frontal, parietal-occipital areas. It has been accepted that low frequency might be involved in the integration across widely spatially large scale networks and high frequency (beta and gamma) oscillations are distributed over a more limited topographic area tuning the local scale network interactions. The coupling between slow and high oscillations has been observed in various regions during rest, the processing of visual and auditory stimuli, memory operations, and working memory maintenance (Palva and Palva, 2007; Roux et al., 2013; Lega et al., 2016; Park et al., 2016). These findings suggest that the slow-fast rhythm interactions play an important role in coordinating information processing. Cross-frequency phase synchrony between alpha, beta and gamma oscillations has been thought to coordinate the selection and maintenance of neuronal object representations during perception, consciousness and working memory (Palva and Palva, 2007). The existence of a beta-delta interaction had been associated with anxiety, a prevalent neuropsychiatric symptom observed in AD patients (Miskovic et al., 2010). Reduced theta/beta ratio may reflect lower reward-gain motivation and higher anxiety levels (Putman et al., 2010). Therefore, in our study, the enhanced couplings between beta and delta/theta might be associated with neuropsychiatric symptoms, whereas the enhanced couplings between alpha and beta might be related to declined memory, cognition and perception in AD patients. In addition, the cross-frequency overcouplings, which reflect enhanced synchronization, might indicate that AD patients need to use more neural resources, especially from non-temporal lobe, to maintain the resting brain state, and the complexity of the neuronal network has been attenuated.

Considering this present study was a preliminary exploration, it had certain limitations. First, likely restricted by the small sample size, we did not observe a marked correlation between the power of cross-frequency coupling and the neurocognitive performance. Second, we failed to use the multiple comparison correction to confirm the statistical significance on each electrode's level. Therefore, in the future, we need to increase our sample size to confirm the abnormality of EEG oscillations in AD patients.

CONCLUSION

In the present study, using wavelet-based EEG analysis, expected for the increased delta and decreased alpha power, an enhanced ongoing gamma rhythm power was found in AD patients. Furthermore, the enhancement of the cross-frequency coupling strength between the beta/gamma and low-frequency bands was observed in AD patients. These current initial observations might provide new evidence for the disturbance of the brain oscillation network in AD and further deepen our understanding of the central mechanisms of AD. Future questions that should be addressed are

whether these alterations are related to certain impairments in AD patients and whether the abnormal dynamics of brain oscillations in some core areas affect the global abnormality.

AUTHOR CONTRIBUTIONS

JW, YF, XW and HY designed the study and collected the data; JW analyzed the data and wrote the manuscript; and HW and XY conceived the study and supervised the work. All authors contributed to the subsequent drafts and approved the final version.

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NeurimmiRs and Postoperative Delirium in Elderly Patients Undergoing Total Hip/Knee Replacement: A Pilot Study

Rui Dong, Lingling Sun, Yayuan Lu, Xi Yang, Mian Peng and Zongze Zhang*

Department of Anesthesiology, Zhongnan Hospital of Wuhan University, Wuhan, China

Objective: Postoperative delirium (POD) is a frequent complication after surgery and its occurrence is associated with poor outcomes. The pathophysiology of this complication is not clear, but identification of risk factors is important for positive postoperative outcomes. The purpose of this study was to investigate the associations between the preoperative expression levels of microRNA (miR)-146a, miR-125b, and miR-181c in cerebrospinal fluid (CSF) and serum and the development and severity of POD.

Methods: Forty elderly patients aged 65 years old and older admitted for elective total hip/knee replacement under spinal anesthesia. Preoperatively, baseline cognitive function was assessed using the Mini-Mental State Examination. Each patient was interviewed daily on the first and second postoperative days. Delirium was diagnosed using the Confusion Assessment Method, and delirium severity was measured using the Memorial Delirium Assessment Scale (MDAS). Preoperative serum and CSF miR levels were determined by quantitative real-time PCR (qRT-PCR).

Results: POD was detected in 27.5% (11/40) of patients. Up-regulation of miR-146a and miR-181c in CSF and down-regulation of miR-146a in serum were observed preoperatively in patients who developed POD, while patients with and without POD did not differ in serum or CSF levels of miR-125b. Delirious patients had higher CSF/serum ratios of miR-146a and miR-181c levels than non-delirious patients. The lower CSF miR-146a and CSF/serum miR-146a ratios were significantly associated with milder POD severity, represented by a lower MDAS score.

Conclusion: The dysregulation of preoperative miR-146a and miR-181c in CSF and serum was associated with the development and severity of POD. These NeurimmiRs might participate in the neuropathogenesis of POD, pending further investigations.

Clinical trial registration: this study was registered at ClinicalTrials.gov (NCT02817386).

Keywords: postoperative delirium, microRNA, neuroinflammation, surgery, elderly patients

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Tao Yang,
University of Michigan, United States

****Correspondence:***
Mian Peng
sophie_pm@msn.com

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INTRODUCTION

Postoperative delirium (POD), an acute, transient, fluctuating disturbance in attention, cognition, and level of consciousness, is a common (15–53%) postoperative complication (Marcantonio et al., 1994; Liu and Leung, 2000; Sieber and Barnett, 2011), and it is associated with longer hospital stays, worse functional outcomes, higher healthcare costs, and increased mortality (Shim and Leung, 2012). However, at the current time, effective prevention and treatment are not only hampered by lack of knowledge about the neuropathogenesis of POD but also by a lack of biomarker(s) that could identify the risk for the development of POD. Neuroinflammation, in particular, has frequently been cited as an important etiological factor associated with the development of POD (van Gool et al., 2010).

Neuroinflammation plays a crucial role in POD (Cerejeira et al., 2010; van Gool et al., 2010). Surgical trauma engages the innate immune system to release proinflammatory cytokines, in particular interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α). These cytokines signals can be transmitted to the brain and lead to neuroinflammation through direct neural pathways (via primary autonomic afferents), transport across the blood–brain barrier (BBB), or entry via the disrupted BBB. Increased brain proinflammatory cytokines can overactivate microglia, which induces further cytokine release in cerebral tissue and fuels a vicious cycle of neuroinflammation (Perry, 2004; Teeling and Perry, 2009). Furthermore, overactivated microglia creates a neurotoxic response, causes neuronal injury, and affects neuronal function, leading to POD (Garden and Moller, 2006).

MicroRNAs (miRs) are endogenous, short, non-coding RNAs. Mature miRs are single-stranded RNA molecules of ∼20-25 nucleotides that act as important post-transcriptional regulators of gene expression by binding with their target mRNAs (Singer et al., 2005; Tan et al., 2013). Several miRs have been shown to modulate both neuronal and immune processes (here called NeurimmiRs; Soreq and Wolf, 2011). Recent findings have demonstrated their important roles in neuroinflammation. For example, in prion disease, a uniquely infectious neurodegenerative condition, miR-146a over-expression has been reported in the brain of prion infected mice concurrent with the onset of prion deposition and appearance of activated microglia (Saba et al., 2012). Additionally, miR-146a has also been shown to be induced in response to inflammatory cues, such as IL-1β, as a negative-feedback regulator of the human astrocyte-mediated inflammatory response (Iyer et al., 2012). In Alzheimer's disease (AD), in which neuroinflammation is a central component, up-regulation of miR-125b was found in the hippocampus and medial frontal gyrus of AD patient (Cogswell et al., 2008). In addition, miR-125b has been reported to repress the expressions of complement factor-H protein (CFH) and interferon regulatory factor 4 (IRF4), which are factors involved in the innate immune system and in the proinflammatory response, in human primary astroglial cells (Lukiw et al., 2012). Moreover, lower levels of miR-181c were found in AD brains, and miR-181c was also down-regulated in the serum of probable AD and mild cognitive impairment (MCI) patients (Geekiyanage et al., 2012). Recent studies have also demonstrated the important roles of miR-181c in the response of astrocytes to inflammatory settings. Over-expression of miR-181c enhanced the LPS-induced increase in interleukin-10 (IL-10) levels, while knockdown of miR-181c resulted in a significant increase in the expression of LPS-induced production of proinflammatory cytokines [IL-1β, TNF-α, interleukin-6 (IL-6), interleukin-8 (IL-8)] and high mobility group box-1 protein (HMGB1) in cultured cortical astrocytes (Hutchison et al., 2013). However, whether these NeurimmiRs are associated with POD remains unknown.

Therefore, the objective of this pilot study was to assess whether the preoperative expression levels of miR-146a, miR-125b, and miR-181c in cerebrospinal fluid (CSF) and serum were associated with POD. We hypothesized that preoperative expression levels of these NeurimmiRs in CSF and serum would be associated with the development and severity of POD. The findings of this investigation may be helpful to create a correlation between the NeurimmiRs expression levels and development of POD, which would promote more studies to investigate the role of NeurimmiRs in the neuropathogenesis of POD and facilitate more miRs biomarker studies of POD.

METHODS

This study was performed in accordance with the Declaration of Helsinki and was approved by the research ethics committee of Zhongnan Hospital of Wuhan University. With written informed consent, we performed a prospective, observational study, which was registered at ClinicalTrials.gov (NCT02817386).

Study Population

The study was conducted at Zhongnan Hospital of Wuhan University (Wuhan, China) between March 2015 and February 2016. Eligible patients were at least 65 years old and were scheduled to have total hip/knee replacement under spinal anesthesia. A total of 86 adults were asked to participate in this study (see **Figure 1**, flow diagram). After reviewing patient medical records, patients were excluded if they had (1) a past medical history of neurological or clinically evident neurovascular disease (e.g., AD, other forms of dementia, stroke); (2) inability to read or severe visual or auditory deficits; (3) Mini-Mental State Examination (MMSE) scores of 26 or less; (4) American Society of Anesthesiologists (ASA) score [a global score that assesses the physical status of patients before surgery, ranging from 1 (normal health) to 5 (moribund) (Davenport et al., 2006)] greater than 3; (5) a history of alcohol abuse and drug dependence; or (6) unwillingness to comply with the protocol or procedures.

Neuropsychological Testing

Each patient was interviewed preoperatively on the first and second postoperative days. The MMSE was administered one day before the scheduled surgery. The assessment of delirium was performed on the first and second days after surgery between 8:00 am and 10:00 am. A visual analog scale (VAS) score of

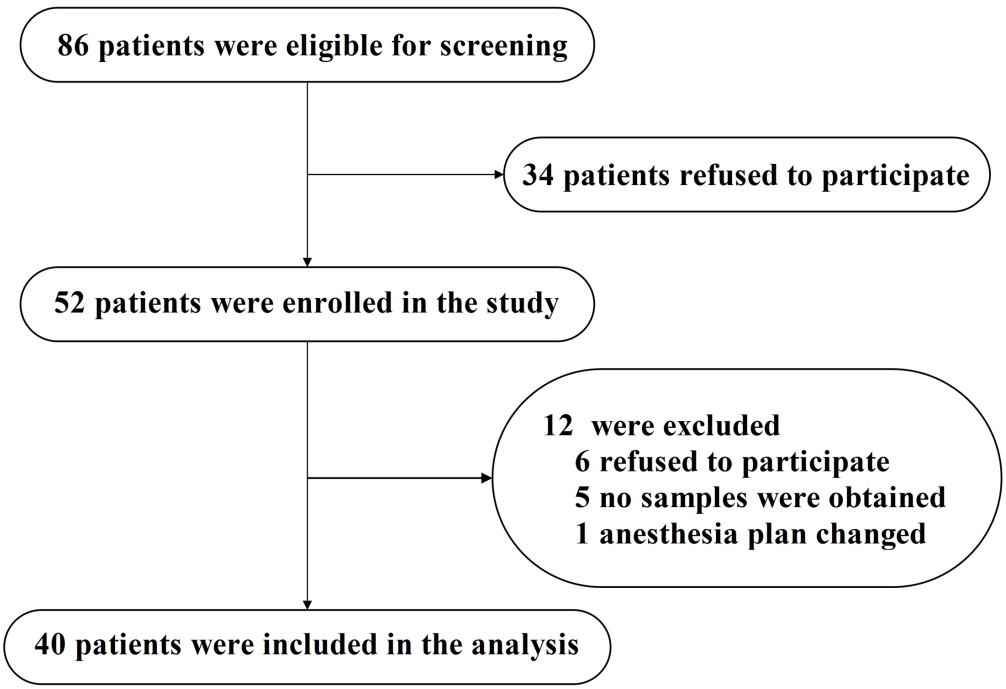

FIGURE 1 | Flow diagram. The flow diagram shows that 86 patients were initially screened for the studies, and 40 patients were finally included in the data analysis.

0–10 (lower score indicating lower level of pain; Chung et al., 2016) was used to assess pain in the patients at the same time. The presence or absence of POD was defined according to the Confusion Assessment Method (CAM), and the severity of POD was defined according to the Memorial Delirium Assessment Scale (MDAS) (Inouye et al., 1990; Schuurmans et al., 2003). The Chinese version of the CAM and MDAS have been proved to have good reliability and validity with use in the Chinese elderly population (Leung et al., 2008; Shi et al., 2014). In this study, the highest CAM and MDAS scores from the postoperative day 1 and day 2 were presented. MDAS scores were evaluated for each patient, regardless of whether he or she met the CAM criteria on that particular day.

Anesthesia and Surgery

All the participants underwent total hip or total knee replacement under spinal anesthesia by the same surgery team to avoid potential confounding factors owing to varying surgery skills or different surgical practices. Electrocardiography, pulse oximetry and non-invasive blood pressure were continuously monitored during anesthesia and were recorded at fixed intervals of 5 min. 37 patients received propofol during the surgery for sedation. The postoperative pain control included standard postoperative pain management, and postoperative analgesia was restricted to non-opioids (flurbiprofen axetil) unless clinically indicated. All the details of clinical care were documented in case report forms.

Sample Collection

Peripheral venous blood samples (5 ml) were collected in additive-free vacuum blood tubes from the enrolled patients before anesthesia. Then, serum specimens were isolated by two steps of centrifugation. The blood samples were centrifuged at 3000 *g* for 10 min in 4°C for the collection of supernatants, followed by centrifuging again at 12,000 *g* for 10 min in 4°C for the collection of pure serum (Tan et al., 2014), which was stored at −80°C until further analysis.

The CSF (4 ml) was collected in an RNase-free Eppendorf tube during spinal anesthesia prior to administration of the local anesthetic. The samples were centrifuged immediately at 3000 rpm at 4°C for 10 min to remove cells (Muller et al., 2014), and only the supernatant was retained at −80° until further analysis.

RNA Extraction, Reverse Transcription, and qRT-PCR

We extracted total RNA from 2 ml of CSF and 300 μl of serum using TRIzol reagent (Invitrogen, CA, USA) in accordance with the manufacturer's protocol. The RNA concentration and purity were detected using a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, USA) (Supplementary Table S3). Our RNA sample purity was between 1.8 and 2.0. At least 600 ng of total RNA of serum or 60 ng for CSF samples was used to perform reverse transcription using stem-loop RT primers for three candidates (miR-146a, miR-125b, miR-181c) and for endogenous control (U6) according to the manufacturer's protocol. U6, which provided the most stabilized expression in both the POD group and the non-POD group samples (**Figure 2A**), was used as an endogenous control for the validation of all the selected candidate miRs. The

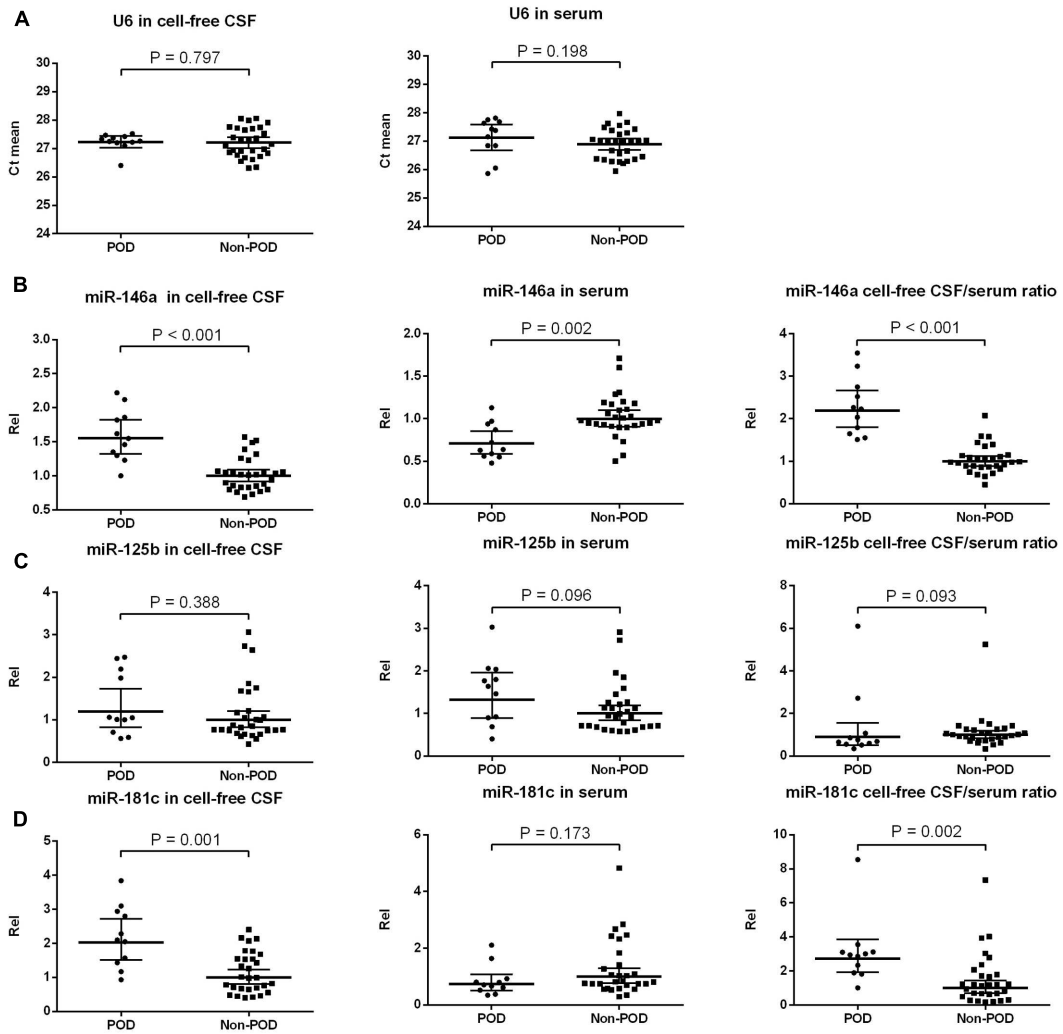

FIGURE 2 | Expression of candidate NeurimmiRs in the CSF and serum of patients with or without POD. Scatter plots of mean Ct-values of U6 **(A)** and expression levels of miR-146a **(B)**, miR-125b **(C)**, and miR-181c **(D)** in the CSF and serum of patients with or without POD. Rel was calculated after normalization using U6 snRNA. The black horizontal lines represent median Rel values ± 95% CIs. Each point represents the mean of triplicate samples. *P*-values were determined using the Mann–Whitney *U*-test. POD, postoperative delirium; Rel, relative expression level; CSF, cerebrospinal fluid.

primer sequences were obtained from Invitrogen Biotechnology Co., Ltd (Shanghai, China) and are listed in **Table 1**. In the preliminary experiment, the single peak was observed in each melting curve for candidate miRs and U6 snRNA, which indicate good primer specificity. Quantitative real-time PCR (qRT-PCR) was performed using a StepOne real-time PCR system (Life technologies, CA, USA) with the SYBR Premix Ex Taq (TaKaRa, Dalian, China) according to the manufacturers' instructions. Each sample was examined in triplicate, and the amounts of the PCR products produced were normalized to the internal control U6. miR expression levels were obtained by relative quantification using the $2^{-\Delta\Delta Ct}$ method. Findings greater or less than 1 were considered to indicate overexpression or underexpression, respectively. All the values were standardized relative to the non-POD values, which were represented as a value of 1.

Statistical Analysis

The data are expressed as the mean ± standard deviation (SD), the median and interquartile range (IQR, 25–75 percentile) or a number (%). POD incidence is presented as a percentage. The Kolmogorov–Smirnov method was used first to test the normality of all the variables. The Mann–Whitney *U*-test was used to analyze the MDAS, VAS, and MMSE scores between the participants who developed POD and those who did not and to determine the differences in CSF and/or serum NeurimmiRs levels between the delirious and non-delirious patients. The Mann–Whitney *U*-test was also used to analyze the differences in MDAS scores between the participants in the first (lowest) quartile of NeurimmiRs levels and the combination of the participants in the second, third, and fourth (highest) quartiles of miR levels. Finally, we applied simple linear regression to determine the associations between the NeurimmiRs levels in

TABLE 1 | Primers sequences for qRT-PCR.

Category	Sequences
miR-146a	RT: 5′-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGAACCCATG-3′
	Forward: 5′-CCTGAGAAGTGAATTCCATGGG-3′
	Reverse: 5′-TGGTGTCGTGGAGTCG-3′
miR-125b	RT: 5′-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGTCACAAGT-3′
	Forward: 5′-CTTCCCTGAGACCCTAACTTGTG-3′
	Reverse: 5′-TGGTGTCGTGGAGTCG-3′
miR-181c	RT: 5′-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGACTCACCG-3′
	Forward: 5′-GAACATTCAACCTGTCGGTGAG-3′
	Reverse: 5′-TGGTGTCGTGGAGTCG-3′
U6	Forward: 5′-CTCGCTTCGGCAGCACAT-3′
	Reverse: 5′-AACGCTTCACGAATTTGCGT-3′

CSF and/or serum and MDAS scores, and we used multiple linear regression to determine the associations after adjustment for age, sex and total RNA concentration. The regression coefficient ± standard error (SE) was used to illustrate the association between NeurimmiRs levels and MDAS scores.

Because this was a pilot study, no power calculations were performed; instead we aimed to recruit the maximum number of patients possible with the resources available, which we estimated to be 40. Statistical significance was set at $P < 0.05$. SPSS statistical software, version 21.0 (SPSS, Inc, Chicago, IL, USA), and GraphPad Prism software, version 6.01 (GraphPad Software, Inc, La Jolla, CA, USA), were used for data analysis.

RESULTS

Participant Characteristics

Eighty-six eligible participants were screened, 52 of whom provided informed consent for the study. Twelve participants were excluded from the study. The reasons for dropouts are shown in **Figure 1**. Therefore, 40 patients ($n = 40$) remained for analysis. The demographic and clinical data of the participants are summarized in **Table 2**, and the characteristics of the excluded participants are shown in Supplementary Table S1.

The incidence of POD observed at either of the two postoperative assessments was 27.5% ($n = 11$ of the 40 patients). Five of 11 patients who developed POD were male. The median of the highest MDAS score of delirious patients was 13 (11–18) (median and 25–75 percentile), which was higher than that of the non-delirious patients [6 (4–7), $P < 0.001$]. The median of the highest MDAS score of all the participants over the first two postoperative days was 7 (5–11). Because Marcantonio et al. (2002) reported that MDAS scores had prognostic significance even in patients without delirium, we assessed the MDAS scores in the entire population and not only in those who developed POD.

Postoperatively, the highest VAS scores did not differ between patients with delirium 2 (1–3) and without delirium [3 (2–4), $P = 0.200$]. For patients who subsequently developed POD, the preoperative MMSE score [27.5 (27–28)] was not significantly different from the score those who did not develop delirium [28.1 (27–29), $P = 0.086$].

Thirty-seven patients received propofol during the operation for sedation. The mean dose of propofol for patients who developed POD (268.6 ± 33.4 mg) was not significantly different from those who did not develop POD (278.2 ± 34.4 mg, $P = 0.432$).

Preoperative NeurimmiRs Levels in CSF and/or Serum and POD

U6 has been used before as an internal control in CSF (Gallego et al., 2012) and serum (Zuberi et al., 2016), and it was equally present in POD and non-POD samples with a small variation across the samples in each group (**Figure 2A**). Therefore, it was used for normalization purposes in the current study. We

TABLE 2 | Characteristics of participants.

	***N* = 40**
Age (year), mean ± SD	73.8 ± 5.9
Male, *n* (%)	18 (45.0)
Years of education, *n* (%)	
0	9 (22.5)
1–9	19 (47.5)
10–13	7 (17.5)
14–17	2 (5.0)
>17	3 (7.5)
Height (cm), mean ± SD	162.4 ± 7.1
Body weight (kg), mean ± SD	61.3 ± 8.3
BMI (kg/m^2), mean ± SD	23.2 ± 2.4
ASA class, *n* (%)	
I	0
II	26 (65.0)
III	14 (35.0)
Time of anesthesia (min), mean ± SD	141.5 ± 17.9
Time of surgery (min), mean ± SD	105.6 ± 17.1
Type of surgery	
Total hip arthroplasty/replacement, *n* (%)	17 (42.5)
Total knee arthroplasty/replacement, *n* (%)	23 (57.5)
Estimated blood loss (ml), median and 25–75 percentile	150 (103–200)
Postoperative the highest CAM score, median and 25–75 percentile	18 (16–23)
Postoperative the highest MDAS score, median and 25–75 percentile	7 (5–11)
Postoperative the highest VAS score, median and 25–75 percentile	3 (1–4)

The length of anesthesia was defined from the time that the anesthesiologists started the spinal anesthesia in the patients to the time when the patients were sent to the post-anesthesia care unit. The length of surgery was defined from the time of initial incision to the time of the closure of the skin. POD, postoperative delirium; ASA, American Society of Anesthesiologists; cm, centimeter; min, minute; kg, kilogram; ml, milliliter; SD, standard deviation; CSF, cerebrospinal fluid.

compared the preoperative levels of three candidate NeurimmiRs (miR-146a, miR-125b, and miR-181c) in CSF and/or serum in the participants with POD and those without it. The Mann–Whitney test showed that patients with delirium had a higher CSF miR-146a level, a lower serum miR-146a level, and a higher CSF/serum miR-146a ratio compared to non-delirious patients (**Figure 2B**). However, no significant difference was observed between patients with or without delirium with regard to miR-125b levels in CSF and serum (**Figure 2C**). Additionally, for patients who ultimately developed POD, the CSF level of miR-181c, as well as the ratio of CSF/serum miR-181c, was significantly increased compared to patients who did not develop delirium (**Figure 2D**). However, patients with and without POD did not differ statistically with regard to the serum levels of miR-181c (**Figure 2D**).

Preoperative NeurimmiRs Levels in CSF and/or Serum and POD Severity

Next, we investigated whether the levels of miR-146a and miR-181c in CSF and serum, as well as the ratios of CSF/serum miR-146a and miR-181c, were associated with POD severity. MDAS has been used to assess the severity of delirium symptoms based on 10 features (Shi et al., 2014). In the current study, MDAS scores were evaluated for each patient, regardless of whether he or she met the CAM criteria, given that MDAS scores had prognostic significance even in patients without delirium (Marcantonio et al., 2002). We first compared the MDAS score, the measurement of delirium severity, between the patients in the first quartile and the patients in the combination of the second, third, and fourth quartiles. We found that the patients in the lowest quartile of CSF miR-146a had lower MDAS scores (**Figure 3A**) than those of the patients in the combination of the second, third, and fourth quartiles of CSF miR-146a. Similarly, the highest MDAS score of the patients in the first quartile of CSF/serum miR-146a ratio was lower than that of the patients in the combination of the second, third, and fourth quartiles of CSF/serum miR-146a ratio (**Figure 3C**). Conversely, the highest MDAS score of the patients in the first quartile of serum miR-146a was higher than that of the patients in the combination of the second, third, and fourth quartiles of serum miR-146a (**Figure 3B**). However, no significant difference in the highest MDAS score was observed between the patients in the first quartile and the patients in the combination of the second, third, and fourth quartiles of CSF miR-181c or CSF/serum miR-181c ratio (**Figures 3D,E**).

Then, we assessed the relationship between the NeurimmiRs levels in CSF and/or serum and MDAS scores. The data were fit by linear regression analysis (**Supplementary Figure S1**) and using unadjusted simple linear regression, we found that the preoperative CSF level of miR-146a, as well as the ratios of CSF/serum miR-146a and miR-181c, were significantly correlated (positively) with the highest MDAS score. However, the preoperative serum level of miR-146a was significantly correlated (negatively) with the highest MDAS score (**Table 3**). Multiple linear regression, after adjusting for age, sex, and total RNA concentration, showed that the preoperative CSF miR-146a level, as well as the ratios of CSF/serum miR-146a and miR-181c, remained significantly correlated (positively) with the highest MDAS score (**Table 3**).

DISCUSSION

In this pilot study, we assessed the associations between preoperative expressions of NeurimmiRs (miR-146a, miR-125b, and miR-181c) in CSF and serum and POD in 52 older adults who underwent total hip and knee replacement under spinal anesthesia. We found up-regulation of miR-146a and miR-181c in CSF and down-regulation of miR-146a in the serum of patients who developed POD. Additionally, the delirious patients had higher CSF/serum ratios of miR-146a and miR-181c levels than the non-delirious patients. We also found that lower CSF miR-146a and CSF/serum miR-146a ratios were significantly associated with milder POD severity, as represented by a lower MDAS score. Taken together, these findings suggested that miR-146a and miR-181c might participate in the neuropathogenesis of POD, pending further investigation.

Previous studies have demonstrated that miRs are stably expressed in various body fluids (Weber et al., 2010), and their unique expression patterns can serve as fingerprints of neurological diseases such as AD (Denk et al., 2015). CSF is in direct contact with the extracellular space of the brain, and it can reflect the biochemical changes that occur in the brain. Therefore, it is the optimal source of POD biomarkers (Xie et al., 2014). Serum is less invasive and more readily available, and circulating miRs are attractive candidates for monitoring central nervous system (CNS) diseases such as AD (Tan et al., 2014). Accordingly, in the present study, we measured the expression levels of miRs in both CSF and serum in patients who underwent total hip and knee replacement under spinal anesthesia. In addition, the CSF/serum ratio has been reported to a useful parameter for the early diagnosis of CNS diseases (Mitchell et al., 2008; Mikecin et al., 2013; Schmidt et al., 2015), and it could exclude the influence of the physiology and pathology of the participants (Mikecin et al., 2013). Thus, we also calculated the CSF/serum ratios of miRs levels in this study.

The incidence of POD following total joint replacement in our study (27.5%) was within the reported range of 3.6–41% (Rudolph and Marcantonio, 2011; Xie et al., 2014; Scott et al., 2015). For example, Xie et al. (2014) reported that POD occurred in 20% of patients ($\geq$63 years old) who underwent total hip and knee replacement under spinal anesthesia. The variation in the POD incidence could be due to age and the influence of perioperative factors, such as postoperative pain (Leung et al., 2013) and sleep disturbances (Leung et al., 2015). Therefore, the incidence of POD (27.5%) in this study demonstrated the validity of our delirium assessment methods. However, in this pilot study, the high dropout rate and small sample size might have resulted in consequent uncertainty about the incidence, and this requires further investigation.

Despite an increase of studies focused on the identifications of POD risk factors, the POD molecular mechanisms are still largely unknown (Maclullich et al., 2008) and notably, the possibility for early identification of patients who may develop POD is still to

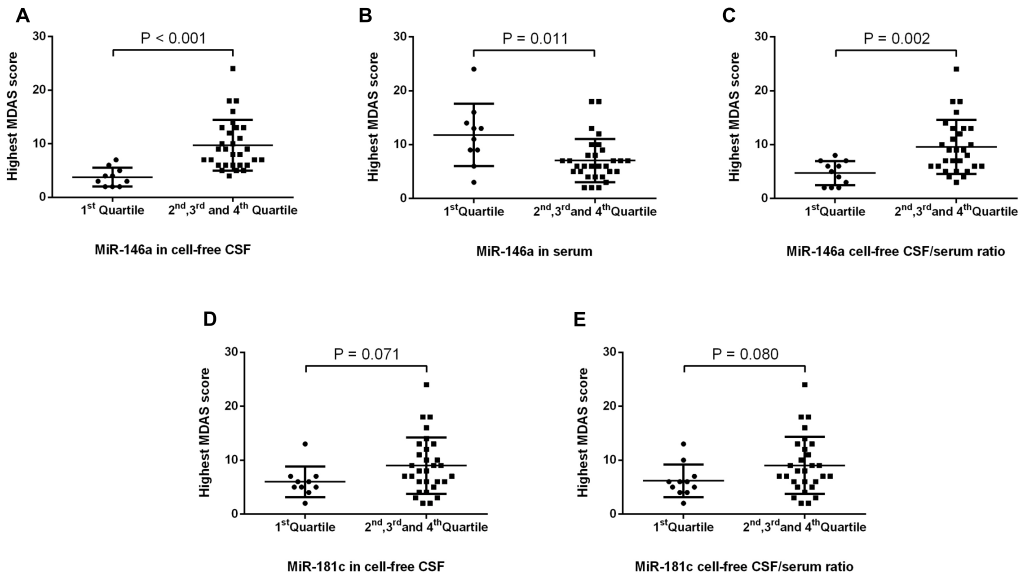

FIGURE 3 | POD severity in the first quartile and the combination of the other three quartiles of levels of miRs and miR CSF/serum ratios. We found that the median of the highest MDAS score (4, 2–5) of the patients in the first quartile of miRNA-146a in CSF was significantly lower than that of the patients in the combination of the second, third, and fourth quartiles of miRNA-146a in CSF (9, 6–13) **(A)**. In contrast, the median of the highest MDAS score (12, 8–14) of the patients in the first quartile of miRNA-146a in serum was significantly higher than that of the patients in the combination of the second, third, and fourth quartiles of miRNA-146a in serum (6, 5–8) **(B)**. The median of the highest MDAS score in the first quartile of miR-146a cell-free CSF/serum ratio (5, 2–7) was significantly lower than that of the patients in the combination of the second, third, and fourth quartiles of miR-146a CSF/serum ratio (9, 6–13) **(C)**. No significant difference in the highest MDAS score was observed between the patients in the first quartile and the patients in the combination of the second, third, and fourth quartiles of CSF miR-181c or CSF/serum miR-181c ratio **(D,E)**. The black horizontal lines represent median MDAS scores ± interquartile ranges. Each point represents the highest MDAS score. *P*-values were determined using the Mann–Whitney *U*-test. POD, postoperative delirium; CSF, cerebrospinal fluid; MDAS, Memorial Delirium Assessment Scale.

be better defined. The neurotransmitters imbalance hypothesis (Alagiakrishnan and Wiens, 2004) and inflammatory hypothesis (Hala, 2007; Cerejeira et al., 2010; van Gool et al., 2010) are the most widely propagated theories for POD neuropathogenesis. POD has been suggested to be related to neuroinflammation (Cerejeira et al., 2010; van Gool et al., 2010), and it is a marker of brain vulnerability. Its occurrence suggests the possibility of underlying neurological disease, such as early or preclinical dementia (Marcantonio et al., 1994; Inouye and Ferrucci, 2006; Davis et al., 2012). Surgery and anesthesia might unmask the underlying pathology (Gunther et al., 2012). In other words, major surgery and anesthesia could be considered a stress test for the brain, with POD as a "positive" result of the test, revealing brain vulnerability. Thus, it is plausible that patients who develop POD have some special underlying changes in the vulnerable brain that facilitate neuroinflammation induced by surgery and anesthesia. In our study, the preoperative changes in miR-146a and miR-181c levels in CSF and serum in patients who developed POD indicated that the deregulation of these NeurimmiRs could be one of these changes in the vulnerable brain.

Increasing evidence has demonstrated the involvement of miR-146a in the regulation of inflammation in human neurological disorders. In physiological conditions, transcription of miR-146a occurs at baseline levels; however, initiation of

TABLE 3 | Correlation between MDAS score and the levels of miRs or ratios.

Highest MDAS score	Unadjusted		Adjusted by age, sex, and total RNA concentration	
	Regression coefficient ± SE	*P*-value	Regression coefficient ± SE	*P*-value
miR-146a in CSF	0.852 ± 1.087	<0.001***	0.872 ± 1.101	<0.001***
miR-146a in serum	−0.400 ± 2.659	0.011**	−0.403 ± 2.750	0.026*
miR-146a CSF/serum ratio	0.817 ± 0.643	<0.001***	0.817 ± 0.652	<0.001***
miR-181c in CSF	0.680 ± 0.698	<0.001***	0.682 ± 0.720	<0.001***
miR-181c CSF/serum ratio	0.307 ± 0.424	0.054	0.302 ± 0.439	0.078

*The left panel of the table illustrates the results of the regression coefficients for miR-146a in CSF, miR-146a in serum, miR-146a CSF/serum ratio, miR-181c in CSF and miR-181c CSF/serum ratio with the highest MDAS score in a simple linear regression. The right panel of the table shows the regression coefficients in multiple linear regressions, including adjustment for confounding factors. MDAS, Memorial Delirium Assessment Scale; CSF, cerebrospinal fluid; SE, standard error, *P < 0.05; **P < 0.01; ***P < 0.001.*

proinflammatory Toll-like receptor (TLR) signaling immediately results in strong co-induction of its expression through a mechanism that is largely NF-κB-dependent (Boldin and Baltimore, 2012). In addition, miR-146a could also be induced as a negative-feedback regulator of the astrocyte-mediated inflammatory response (Iyer et al., 2012). Furthermore, in AD patients, miR-146a has been shown to down-regulate CFH, which is an important repressor of innate immunity acting on the cerebral inflammation response (Lukiw and Alexandrov, 2012; Lukiw et al., 2012). Similarly, miR-181c plays important roles in the response to inflammatory settings. It negatively regulates the production of multiple cytokines and fibroblast growth factor 2 (FGF2) in astrocytes, effectively suppressing their production in an inflammatory environment (Hutchison et al., 2013). miR-181c can also directly regulate TNF-α and TLR4 production post-transcriptionally, inhibiting NF-κB-mediated inflammation (Zhang et al., 2012, 2015; Hutchison et al., 2013). Collectively, these NeurimmiRs (miR-146a and miR-181c) have been implicated in the regulation of the immune and inflammatory responses. It is plausible that their abnormal expression in the CSF and serum of patients with POD might reflect a low-level chronic inflammatory state in the vulnerable brain before surgery. Surgical procedures can trigger systemic inflammation (Dantzer et al., 2008; Cerejeira et al., 2010; MacLullich et al., 2011), exaggerate neuroinflammation in the primed vulnerable brain and lead to delirium (Murray et al., 2012). Aging and neurodegenerative diseases are well-known predisposing risk factors for delirium (Inouye and Charpentier, 1996), and they are also accompanied by a low-level chronic inflammatory state (Olivieri et al., 2013). Bhaumik et al. (2009) found that some miRs, for example, miR-146a expression significantly increased during senescence of human fibroblasts. In our study, we focused on patients who were at least 65 years old (mean age: 73.8 ± 5.9 years). Therefore, it is possible that the presence of miR-146a in patients without POD was aging based.

In our study, the up-regulation of miR-146a and miR-181c in CSF and the down-regulation of miR-146a in serum were observed in patients who developed POD, while no difference was observed between patients with or without POD with regard to miR-125b levels in CSF and serum. Up-regulation of miR-146a has been reported in the brains of human beings and in mouse models of prion disease (Saba et al., 2008), consistent with our results. However, miR changes in POD have not always been consistent among studies of neuroinflammation-related diseases. For example, in contrast to our observations, recent studies have reported reduced levels of miR-146a and miR-125b in both the serum and CSF of AD patients (Kiko et al., 2014; Muller et al., 2014) and reduced miR-181c in the serum of probable AD and MCI patients (Geekiyanage et al., 2012). Such discrepancies could originate from study-related parameters, such as variations in sample size, type of disease and patient profiles. Interestingly, in our studies, miR-146a and miR-181c expression levels differed between CSF and serum. This outcome was not surprising, given that the miRs in CSF are derived from neural cells, whereas serum miRs are collected from all of the tissues in the body (Burgos et al., 2013). Thus, do serum miRs have crosstalk with CSF miRs? It is unlikely that miRs alone can cross the BBB (Burgos et al., 2013). However, it has been reported that exosomes, which are secreted from cells (Street et al., 2012; Raposo and Stoorvogel, 2013) and facilitate intercellular communication by transporting molecules, such as miRs (Duijvesz et al., 2011; Kharaziha et al., 2012; Hannafon and Ding, 2013), can cross the BBB (Alvarez-Erviti et al., 2011). The study by Yagi et al. (2017) demonstrated that miR enrichment in the exosomal fractions relative to the non-exosomal fractions of both CSF and serum and miR expression profiles in exosome fractions differed between CSF and serum. In particular, the dominantly expressed exosomal miRs were very different between CSF and serum. These results suggested that the brain is a major source of CSF exosomal miRs, although a small fraction of CSF exosomal miRs absent from the brain might have been derived from leucocytes in CSF (Gombar et al., 2012). Importantly, these observations also suggested that exosomal miR translocation between the blood and CSF could be rare. However, the communication of exosomal miRs between CSF and serum could be affected and could vary under pathological conditions, especially in diseases affecting BBB function (Yagi et al., 2017). However, to date, the causal relationship between BBB permeability and POD remains uncertain, although Acharya et al. (2015) reported that inhaled anesthetics, such as sevoflurane and isoflurane, act directly on brain vascular endothelial cells to increase BBB permeability, thereby contributing to POD. Therefore, future studies to investigate the communication between miRs in CSF and serum are warranted.

In comparison with sevoflurane anesthesia, propofol anesthesia has been shown to be associated with a lower incidence (6.9%) of POD in elderly patients (Ishii et al., 2016). In the current study, the mean dose of propofol for patients who developed POD was not significantly different from those who did not develop POD. Therefore, these results suggest that propofol sedation may not significantly affect the development of POD, pending further investigations.

In the current study, we not only applied the MMSE to exclude participants with dementia, but we also compared differences in the MMSE at baseline between the participants with or without POD. We found that, for patients who subsequently developed POD, the preoperative MMSE score was not significantly different from that of subjects who did not develop delirium. However, it is known that prior cognitive impairment is a major risk factor for delirium (Davis et al., 2015). Moreover, delirium risk in the elderly population is indirectly proportional to baseline MMSE score. For instance, the probability of incident delirium at follow-up for an 85-year-old man with MMSE = 28 points at baseline would be 0.12, increasing to 0.29 for an equivalent individual with an MMSE score of 10 points at baseline (Davis et al., 2015). These discrepancies could be explained by issues of the small sample size and the ceiling effects of the MMSE (Xu et al., 2002).

There were some potential limitations of our study. First, the current pilot study was not sufficiently powered to provide strong evidence for the role of NeurimmiRs in POD due to the small sample size and high dropout rate. A larger study with adequate power is indicated to validate our results. Second, we removed the cells from the CSF according to the methods as described by Muller et al. (2014), considering that the influence of blood

contamination on CSF miR levels is a potential confounding factor. However, the presence of blood cells in CSF, even if they are removed using centrifugation before analysis, can lead to bias in the expression levels of miRs (Muller et al., 2014). Therefore, to avoid any bias in the results, we should determine the number of blood cells in CSF samples when measuring miR levels in future studies. Third, we measured delirium only once daily; given the fluctuating nature of delirium, we might have underestimated its incidence. Fourth, only one internal control (snRNA U6) has been used in the current study. We should use more controls in the further investigations. Finally, NeurimmiRs play a significant role in the pathophysiological context, especially in the neuroinflammatory process and neurodegenerative diseases (Supplementary Table S2). In this study, we just focused on three of them: miR-146a, miR-125b, and miR-181c. However, there might be more NeurimmiRs, such as miR-124 and miR-132, that could contribute to neuroinflammation (Soreq and Wolf, 2011) and the neuropathogenesis of POD. We propose that the specific serum and CSF miR expression profiles [not a single miR or a few miR(s)] constitute the fingerprint of POD, which could have an enormous impact on diagnosis and personalized medicine in the future.

In summary, dysregulation of preoperative miR-146a and miR-181c in CSF and serum was associated with the development and severity of POD. To date, it remains unknown whether there is a causal relationship or an association between these NeurimmiRs expression levels and the development of POD. Hence, further studies are required to clarify this question. These studies will also hopefully facilitate miRs biomarker studies of POD.

AUTHOR CONTRIBUTIONS

RD contributed to study design, data collection, statistical analysis, and manuscript preparation. LS performed qRT-PCR. YL involved in data collection. XY performed neuropsychological testing. MP contributed to study concept and design, manuscript preparation and review. ZZ performed statistical analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00200/full#supplementary-material

FIGURE S1 | CSF miR-146a expression level and MDAS scores data test results.

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Genetics of Aggression in Alzheimer's Disease (AD)

Walter J. Lukiw[1,2,3,4]* *and Evgeny I. Rogaev*[5,6,7,8]

[1]*Louisiana State University (LSU) Neuroscience Center, Louisiana State University Health Science Center, New Orleans, LA, USA,* [2]*Department of Ophthalmology, Louisiana State University Health Science Center, New Orleans, LA, USA,* [3]*Department of Neurology, Louisiana State University Health Science Center, New Orleans, LA, USA,* [4]*Bollinger Professor of Alzheimer's disease (AD), Louisiana State University Health Sciences Center, New Orleans, LA, USA,* [5]*Vavilov Institute of General Genetics, Russian Academy of Sciences, Moscow, Russia,* [6]*Center for Brain Neurobiology and Neurogenetics, Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia,* [7]*Department of Psychiatry, Brudnick Neuropsychiatric Research Institute, University of Massachusetts Medical School, Worcester, MA, USA,* [8]*School of Bioengineering and Bioinformatics, Lomonosov Moscow State University, Moscow, Russia*

Alzheimer's disease (AD) is a terminal, age-related neurological syndrome exhibiting progressive cognitive and memory decline, however AD patients in addition exhibit ancillary neuropsychiatric symptoms (NPSs) and these include aggression. In this communication we provide recent evidence for the mis-regulation of a small family of genes expressed in the human hippocampus that appear to be significantly involved in expression patterns common to both AD and aggression. DNA array- and mRNA transcriptome-based gene expression analysis and candidate gene association and/or genome-wide association studies (CGAS, GWAS) of aggressive attributes in humans have revealed a surprisingly small subset of six brain genes that are also strongly associated with altered gene expression patterns in AD. These genes encoded on five different chromosomes (chr) include the androgen receptor (AR; chrXq12), brain-derived neurotrophic factor (BDNF; chr11p14.1), catechol-O-methyl transferase (COMT; chr22q11.21), neuronal specific nitric oxide synthase (NOS1; chr12q24.22), dopamine beta-hydroxylase (DBH chr9q34.2) and tryptophan hydroxylase (TPH1, chr11p15.1 and TPH2, chr12q21.1). Interestingly, (i) the expression of three of these six genes (COMT, DBH, NOS1) are highly variable; (ii) three of these six genes (COMT, DBH, TPH1) are involved in DA or serotonin metabolism, biosynthesis and/or neurotransmission; and (iii) five of these six genes (AR, BDNF, COMT, DBH, NOS1) have been implicated in the development, onset and/or propagation of schizophrenia. The magnitude of the expression of genes implicated in aggressive behavior appears to be more pronounced in the later stages of AD when compared to MCI. These recent genetic data further indicate that the extent of cognitive impairment may have some bearing on the degree of aggression which accompanies the AD phenotype.

Keywords: aggression-Alzheimer's disease (AD), retrogenesis and schizophrenia, androgen receptor (AR), brain derived neurotrophic factor (BDNF), tryptophan hydroxylase (TPH), neuronal specific nitric oxide synthase (NOS1), catechol-O-methyl transferase (COMT), dopamine beta-hydroxylase (DBH)

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***Correspondence:**
Walter J. Lukiw
wlukiw@lsuhsc.edu

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INTRODUCTION

There are currently 5.4 million Americans afflicted with Alzheimer's disease (AD) and one in nine Americans (11.1%) over the age of 65 have AD[1]. In the later stages, about 45% of all AD patients exhibit hostility and aggression towards their fellow patients, caregivers and/or families (Borroni et al., 2010; Ballard and Corbett, 2013; Fernàndez-Castillo and Cormand, 2016; Liu et al., 2016; Macfarlane and O'Connor, 2016; Wharton et al., 2016). Aggressive behaviors in AD represent a significant public healthcare concern and a social and clinical challenge for institutionalized healthcare. The aggression associated with AD is expressed as an overt and/or often harmful social interaction with the primary intention of inflicting damage or other unpleasantness upon other individuals that may occur either without provocation or in retaliation. Aggressive behavior in AD: (i) can take a variety of neuropsychiatric (NPS) forms; (ii) may be communicated verbally or non-verbally; or (iii) may be expressed physically. There are often multiple forms of aggression in the AD patient including defensive (fear-induced) aggression, predatory aggression, dominance aggression, inter-male aggression, resident-intruder aggression, maternal aggression, sex-related aggression, territorial aggression, isolation-induced aggression and irritability-associated aggression (Fernàndez-Castillo and Cormand, 2016; Liu et al., 2016; Macfarlane and O'Connor, 2016; Wharton et al., 2016). Clinical and social aspects of these types of AD-associated aggression are the subject of several recent excellent reviews and include the most up-to-date pharmacological strategies and therapeutic advances to specifically address the aggressive AD phenotype (Ballard and Corbett, 2013; Fernàndez-Castillo and Cormand, 2016; Liu et al., 2016; Macfarlane and O'Connor, 2016; Wharton et al., 2016). This original research article provides new data on the overlap in the expression of brain-enriched genes in AD with those implicated in aggression and incorporates the findings of the most recent peer-reviewed research on emerging concepts of the genetics linked to aggression in AD.

MATERIALS AND METHODS

Brain Sample Selection and Quality Control

Brain tissues were used in accordance with the institutional review board (IRB)/ethical guidelines at the Louisiana State University Health Sciences Center (LSUHSC) and the donor institutions, and CERAD/NIH criteria were used to categorize all AD tissues in accordance with established guidelines (Cui et al., 2005, 2010; Lukiw et al., 2008; Montine et al., 2016). We used mRNA expression profiles and DNA-array data from a study of 12 mild-cognitively impaired (MCI) subjects (N = 12) and their controls (N = 12), and 12 age-matched sporadic AD hippocampal CA1 (N = 12) and their controls (N = 12). DNA array data was performed using state-of-the-art microfluidics hybridization platforms through an ongoing collaboration with Drs. Cristoff Eicken, Chris Hebel, Jason Mulcahey and Kyle Navel at LC Sciences (Houston, TX, USA); mRNA expression profiles and trends were independently corroborated and verified using RT-PCR or Northern blotting in previously published work from this lab (Cui et al., 2005, 2010; Lukiw et al., 2008; Bhattacharjee et al., 2016). Both the MCI and AD groups had their own control groups because of the age-differences between MCI and AD and our understanding that age is the most significant risk factor for the development of AD (**Table 1**). All control, MCI and AD samples had the incidence of disease verified by post-mortem evaluation; there were no significant differences in age, gender, drug history, total RNA yield, RNA quality, RNA integrity numbers (RIN) amongst the three groups (see **Table 1**).

Expressed Genes Involved in AD and Aggression

The data derived from our DNA/mRNA transcriptomic array analysis were correlated and compared with those of a very recent article by Fernàndez-Castillo and Cormand (2016) who studied aggressive behavior in humans through the analysis of genes and pathways identified via candidate gene association and/or genome-wide association studies (CGAS, GWAS). Only genes of the highest significance, either up-or-down-regulated, were selected for further study, analysis and interpretation. Just six genes were found to most significantly overlap in the incidence of AD and aggression and these included the androgen receptor (AR; chrXq12), brain-derived neurotrophic factor (BDNF; chr11p14.1), catechol-O-methyl transferase (COMT; chr22q11.21), neuronal specific nitric oxide synthase (NOS1; chr12q24.22), dopamine beta-hydroxylase (DBH chr9q34.2) and tryptophan hydroxylase (TPH1, chr11p15.1 and TPH2, chr12q21.1; **Figure 1**).

RESULTS

Table 1 describes the case group (control for MCI **(C1)**, MCI, control for AD **(C2)** and AD), mean and 1 SD of age, post-mortem interval (PMI), senile plaque (SP) and neurofibrillary tangle (NFT) density and RNA quality control parameters and RNA yield for the samples analyzed. There were no significant differences in mean age, PMI, gender, RNA quality control or RNA yield between MCI or AD and their controls; MCI displayed 2.7–4 times the density of SP and NFT as its control **(C1)**; AD displayed 6.1–10 times the density of SP and NFT as its control **(C2)**; $p < 0.05$ (ANOVA); all samples were of the highest purity available from multiple sources of post-mortem brain human samples (Cui et al., 2005; Lukiw et al., 2008; Zhao et al., 2016). High quality RNA samples were subsequently analyzed using mRNA transcriptomic arrays employing μParaflo® Microfluidic Biochip Technologies that interrogate the abundance and speciation of ∼27,000 human mRNAs (LC Sciences, Houston, TX, USA); digitized data were presented in the form of cluster diagrams (Cui et al., 2005; Lukiw et al., 2008); **Figure 1A** describes the results in a color-coded cluster diagram of the most changed genes in

[1]http://www.alz.org/facts/?utm_source=google&utm_medium=search&utm_campaign=google-grants&set.custom.wt=google-grants&gclid=CIjO58yy79ICFUm2wAodlBIGmQ

TABLE 1 | Summary of tissues used from each case group in this study.

Case group	*N*	Age*[1] x ± SD	Age*[1] range	PMI*[2] range	SP/NFT*[3]	RNA $A_{260/280}$	RNA 28S/18S	RNA yield*[4]
C1	12	64.1 ± 8.1	64–78	2.5–3.5	1/3	2.07–2.15	1.45–1.55	1.15–1.35
MCI	12	64.8 ± 8.6	61–71	2.6–3.7	4/8	2.08–2.16	1.45–1.6	1.15–1.42
C2	12	71.5 ± 9.0	63–77	1.1–4.3	1/3	2.05–2.15	1.45–1.6	1.12–1.42
AD	12	72.1 ± 7.5	65–79	1.1–4.2	10/18	2.08–2.12	1.45–1.5	1.05–1.51

*N = number of cases; age is age at time of death; x ± SD = mean plus or minus one standard deviation; age range refers to ranges of the individual age means; post-mortem interval (PMI; death to brain freezing interval) range is the mean range in hours; SP/NFT, respectively senile plaque and neurofibrillary tangle counts, are average lesion densities per square millimeter; RNA $A_{260/280}$ and RNA 18S/28S ratios are indicative of high brain tissue RNA spectral quality; there was no significant difference amongst control, MCI or AD total RNA yield; characterization of control, MCI and AD total RNA message; *[1]years; *[2]death to brain freezing interval in hours at −81°C; *[3]senile plaque (SP) and neurofibrillary tangle (NFT) counts are the mean lesion density per square millimeter (N = 12); *[4]average yield in total ug RNA/mg wet weight brain tissue; hippocampal CA1 tissue samples were male or female Caucasian.*

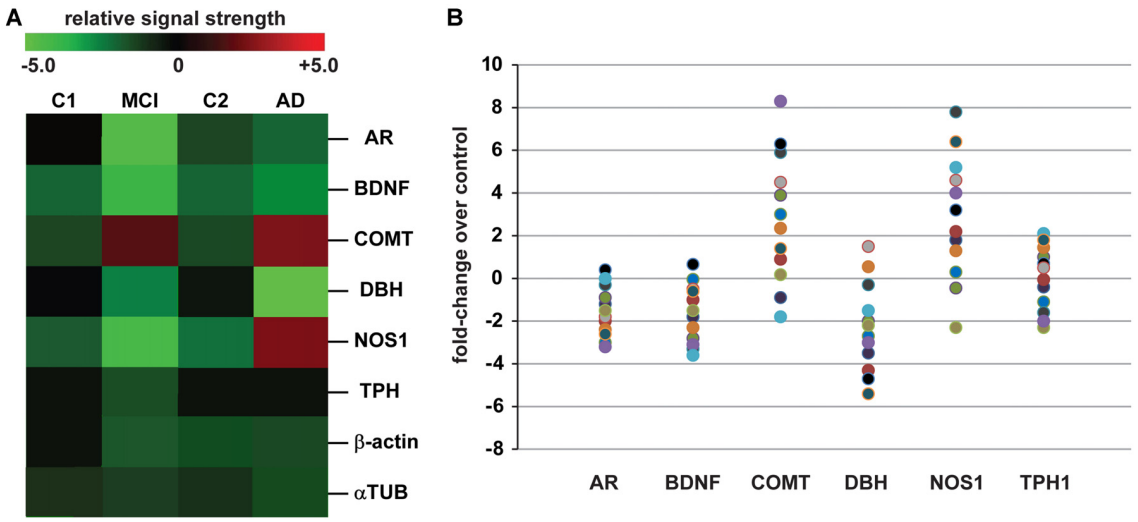

FIGURE 1 | Analysis of expressed genes common to both Alzheimer's disease (AD) and aggression. (A) mRNA transcriptomic arrays were used to quantify the levels of some of the most mis-regulated genes in mild-cognitive impairment (MCI) and AD brain samples compared to an MCI control **(C1)** and an independent AD control **(C2)**; these were compared to unchanging β-actin and/or α-tubulin (αTUB) levels in the same sample; gene expression patterns were next compared to those also mis-regulated in "*the aggressive phenotype*" as recently reported by Fernàndez-Castillo and Cormand (2016); expressed gene alterations common to both AD and aggression included the androgen receptor (AR), brain-derived neurotrophic factor (BDNF), catechol-O-methyl transferase (COMT), dopamine beta-hydroxylase (DBH), nitric oxide synthase (NOS1) and tryptophan hydroxylase (TPH1 shown); genes including COMT and NOS1, and TPH1 to a lesser extent, exhibit increased expression in the transition from MCI to AD; for example TPH1 showed a modest 0.2-fold increase in expression AD over MCI while NOS1 and COMT displayed 2.8- and 2.9-fold increases in expression ($p < 0.05$, ANOVA); data for C1, C2, MCI and AD $N = 12$ cases each; the magnitude of expression for each AD case is quantified in **(B)** for all 12 samples studied; great care was taken in the selection of control and age-matched AD samples; all brain samples were from the hippocampal CA1; there were no significant differences in age, age range, gender, post-mortem interval (PMI) range, or RNA quality between the two groups **(Table 1)**; in **(B)** data for AR, BDNF, COMT, DBH, NOS1 and TPH1 are compared to controls for each sample **(Table 1)**; interestingly, genes such as COMT, BDNF and NOS1: (i) exhibit a trend for wider variation in their expression from sample to sample, and this is in agreement with reports of both up-and down-regulation of their abundance in the literature (see above); and (ii) COMT and NOS1 display the largest general trend for up-regulation in AD vs. control **(C2)**; DBH exhibits a general trend for down-regulation **(A)**. Genechip data for **(B)** is given in Supplementary data in Table S1. Other relevant DNA array data for these and other genes expressed in AD and age-matched controls from our laboratories have been previously published (Colangelo et al., 2002; Cui et al., 2005; Lukiw et al., 2008). Ongoing future studies will benefit from larger sample sizes, more homogeneous phenotypes and standardized measurements to identify expressed genes that underlie aggressive behaviors which accompany the AD process.

MCI or AD vs. controls for an overlapping family of brain genes involved in aggressive behaviors (Fernàndez-Castillo and Cormand, 2016). These genes include AR, BDNF, COMT, DBH, NOS1and TPH1 (TPH2 was not analyzed in these assays). Individual AD signal yield expressed as fold-change over controls are described in a scatter plot in **Figure 1B**. Individual values >0 indicate up-regulation of expression and values <0 indicate decreased expression. Interestingly, the AR, BDNF and TPH1 gene expression patterns all displayed a smaller general variability vs. a wider variability in the expression of genes for COMT, DBH and NOS1 in the AD brain (**Figure 1B**). This may explain, for example, reports on both up- and down-regulated expression of COMT, DBH and NOS1 in the AD brain (see below). The following is a brief discussion of these six genes and their relevance to aggression and AD, highlighting recent advances, particularly within the last 10 months, in this understudied research area.

DISCUSSION

Androgen Receptor (AR, ANDR; chrXq12)

Circulating sex steroidal hormones such as testosterone that play overlapping roles in cognition and aggression have been widely implicated in the etiopathology of AD. While the AR is abundantly expressed in both sexes, in AD expression of the AR has been found to be generally down-regulated, especially in aging males (Butchart et al., 2013; Dart et al., 2013; Fedotova et al., 2016; Jia et al., 2016). Interestingly the steroid-hormone testosterone-activated transcription factor-signaling AR (ANDR) is known to exert regulatory effects on synaptic plasticity and improve cognitive deficits in AD patients and transgenic rodent models for AD (TgAD) but the underlying mechanisms of androgenic action on cognitive performance remain unclear. Testosterone, via the AR, increases synaptophysin expression and improves synaptic plasticity and cognitive metrics in both Aβ42 peptide-hippocampal injected male rats and in the senescence-accelerated mouse prone 8 (SAMP8) TgAD murine model (Huo et al., 2016; Jia et al., 2016). In a recent double-blind, placebo-controlled, between-subject designed study, exogenous administration of testosterone to healthy adult men potentiated the AR-enriched hippocampus, amygdala and hypothalamus—anatomical regions known to be involved in the stimulation of aggressive behavior (Carré et al., 2016). Several studies have further suggested that new treatments targeted toward preventing synaptic pathology in AD or in TgAD models may involve the use of androgen agonists and/or AR-acting drugs (Jia et al., 2016; Pan et al., 2016). Interestingly, polyprenol bioregulators such as *Ropren* (already used in AD treatment in Russia and Australia) and polyprenol 2,3-dihydro derivatives known as "*dolichols*" in gonadectomized rodents exhibit decreased 5-hydroxyindoleacetic acid (5-HIAA)/5-HT ratios in the hippocampus compared with DA and serotonin (5-HT) levels, and are associated with increased anxiolytic (antianxiety) behaviors in treated animals (Sugden et al., 2009; Fedotova et al., 2016). Therefore it may be able to design useful drugs that are able to negate aggression while promoting other useful aspects of testosterone and AR signaling including improvement in cognitive function.

Brain-Derived Neurotrophic Factor (BDNF; chr11p14.1)

BDNF is the most widely distributed neurotrophin in the human CNS and plays several pivotal roles in neural development, survival, synaptic plasticity and cognition. This 247 amino acid neurotrophin participates in axonal growth, pathfinding and in the modulation of dendritic growth and morphology, is a master regulator of synaptic plasticity and thus plays a key role in memory formation and storage (Faria et al., 2014; Nagata et al., 2014, 2016; Song et al., 2015). Therefore, the involvement of BDNF in dementia has been extensively investigated, and several reports indicate that BDNF expression is decreased in hippocampus and neocortex of AD brains (**Figure 1**; Peng et al., 2005; Song et al., 2015). Interestingly, children with severe autism and aggression over-express the AD-relevant beta-amyloid precursor protein (βAPP) at two or more times the levels of children without autism and up to four times more than children with mild autism; βAPP-derived Aβ peptides can directly inhibit the proteolytic conversion of BDNF from pro-BDNF thus reducing its levels (Sokol et al., 2006; Tanila, 2017). Aβ peptides indirectly affect BDNF signaling at synapses by interfering with its axonal transport in part via interaction with the TrkB receptor (Durany et al., 2000; Tanila, 2017). That BDNF expression is associated with multiple independently-regulated promoters suggest that this unique genomic structure may provide flexibility to regulate BDNF signaling in distinct cell types and circuits that serve distinct molecular functions some of which may be involved in aggressive behaviors (Spalletta et al., 2010; Faria et al., 2014; Maynard et al., 2016). It is interesting to speculate that episodic or oscillatory forms of BDNF expression in AD may correlate with aggressive outbreaks or contribute to them via complex neurotrophic signaling pathways that are known to impact behavioral phenotype.

Catechol-O-Methyl Transferase (COMT; chr22q11.21)

COMT catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters DA, epinephrine and norepinephrine, resulting in one of the major degradative pathways of the catecholamine transmitters. COMT appears to play a prominent role in AD pathophysiology by affecting the metabolism of catecholamine neurotransmitters such as DA in the prefrontal cortex which are involved in working memory and executive functioning (Serretti and Olgiati, 2012). Similarly, COMT and DBH are directly involved with DA metabolism; this neurotransmitter system appears to be specifically targeted by the AD process (Martorana and Koch, 2014). While levels of COMT in sporadic AD appear to be highly variable, either up- or down-regulated, meta-analysis studies have identified a possible association between AD and the COMT Val158Met polymorphism in Asian but not in European populations (Lee and Song, 2014; Sauerzopf et al., 2017). More recent and comprehensive meta-analysis involving a review of 10 independent studies, which contained a total of 2777 AD cases and 2829 controls indicated that the COMT Val158Met polymorphism is associated with a decreased risk of AD in the Asian population, but not in the Caucasian or overall populations (Yan W. et al., 2016). Interestingly, genetic risk score based on the accumulation of multiple risk alleles in BDNF, COMT and APOE for AD combining multiple genetic influences may be more useful in predicting late-life cognitive impairment than individual polymorphisms (Wollam et al., 2015). As for other neurotrophins and neurotransmitters such as NOS1, periodic fluctuations in COMT expression in AD may correlate with aggressive behaviors and contribute to "*behavioral dys-homeostasis*" via complex and highly interactive neurotrophic signaling pathways that contribute to NPS events (Perroud et al., 2010; Clelland et al., 2016).

Interestingly, prefrontal and temporal lobe dysfunction and mutations in the COMT gene have been linked to agitation and aggression in patients with schizophrenia, and deficits in cognitive function predispose patients with AD to agitation (Sachs, 2006; Clelland et al., 2016; Yan P. et al., 2016; Yan W. et al., 2016).

Dopamine β-Hydroxylase (DBH; chr9q34.2)

Dopamine beta-hydroxylase (DBH), an oxidoreductase belonging to the copper-requiring type II, ascorbate-dependent monooxygenase family and present in the synaptic vesicles of postganglionic sympathetic neurons exists in both soluble and membrane-bound forms, depending on the absence or presence, respectively, of a signal peptide (Herrmann et al., 2004; Godar and Bortolato, 2014; Ross et al., 2015; Godar et al., 2016). DBH converts DA to norepinephrine (Ross et al., 2015). Like COMT and NOS1, DBH exhibit wide inheritable inter-individual variability in AD that is under genetic control (**Figure 1**; Mustapic et al., 2013; Ross et al., 2015). Decreases in DBH activity found in the early stages of AD may be a reflection of loss of noradrenergic (NA) neurons, and the treatment of early AD patients with selective NA reuptake inhibitors may be indicated in early stages of AD to compensate for loss of NA activities (Mustapic et al., 2013). The highly complex and interactive nature of neurotrophins and neurotransmitters in aggressive behaviors are underscored by recent observations that serotonin and DA interactions in the prefrontal cortex, along with other biological factors such as norepinephrine and testosterone have been found to contribute to the aggressive phenotype, as has monoamine oxidase A (MAOA) that catalyzes the degradation of brain serotonin, norepinephrine and DA (Haavik et al., 2008; Godar et al., 2016).

Neuronal Specific Nitric Oxide Synthase (NOS1; chr12q24.22)

NOS1, a family of NO synthases which synthesize NO from L-arginine is a pivotal mediator in neurotransmission, spatial learning and cognition and has been repeatedly implicated in the neurotoxicity associated with stroke and neurodegenerative disease (Wultsch et al., 2007; Freudenberg et al., 2015; Austin and Katusic, 2016; Miszczuk et al., 2016; Wang et al., 2016). Interestingly, NO is a gaseous neurotransmitter that has also been implicated in a wide range of pathological behaviors including aggression, anxiety, depression and cognitive functioning. NOS1 knockdown mice display a characteristic behavioral profile consisting of reduced anxiety and aggression and impaired cognitive metrics including learning and memory (Wultsch et al., 2007; Miszczuk et al., 2016; Zhou et al., 2016). Recent studies have shown that deficits of endothelial NOS1 in AD play an important role in the phosphorylation of the AD-related lesion tau in murine APP/PS1 TgAD models (Austin and Katusic, 2016) while increased NOS-1 activity and NO transmission in the hippocampus was evidenced to modulate aggression (Miszczuk et al., 2016; Zhou et al., 2016). Again, the seemingly multiphasic bioavailability of NOS1 like that for COMT provides an equally oscillatory potential for episodic and complex behaviors such as aggression against a background of the inflammatory neurodegeneration and disorganized thinking that in part characterize cognitive disruption in AD.

Tryptophan Hydroxylase (TPH1, chr11p15.1; TPH2, chr 12q21.1)

TPH catalyzes the first and rate limiting step in the biosynthesis of the monoamine hormone, neurotransmitter and neuromodulator serotonin (3-(2-aminoethyl)-1H-indol-5-ol, 5-hydroxytryptamine; 5-HT). Remarkably, about 90% of the human body's total serotonin (and hence TPH biosynthetic systems) are located in the neuroendocrine entero-chromaffin cells in the human gastrointestinal (GI) tract, where it is used to regulate intestinal movements and participate in GI-neural tract signaling; the other 10% is synthesized by serotonergic neurons of the CNS where it functions in the regulation of neurite outgrowth, somatic morphology, growth cone motility, synaptogenesis, and control of dendritic spine shape and density, and behaviorally anger, aggression, mood, body temperature, appetite, sleep, pain and cognition. Serotonin acts via a heterogenic receptor family that includes G protein-coupled receptors and ligand-gated ion channels (New et al., 1998; Craig et al., 2004; Shearer et al., 2016; Wirth et al., 2016). TPH is encoded by two separate enzymes: TPH1 produces serotonin in the pineal gland and entero-chromaffin cells, while TPH2 produces serotonin in the Raphe nuclei of the brain stem and myenteric plexus. Interestingly, serotonin is phylogenetically the oldest neurotransmission system present involved in cognition and memory in both vertebrate and invertebrate species, and pathological alterations in 5-HT metabolism and/or down-regulation of serotonergic signaling have been associated with various pathophysiological conditions in the CNS including amyloidogenesis and SP formation, hyper-phosphorylation of tau and NFT formation, two classical aggregates that in part characterize AD brain neuropathology (McClam et al., 2015; Panza et al., 2015; Butzlaff and Ponimaskin, 2016; Wirth et al., 2016). Due to the extensive serotonergic denervation observed in AD and the important roles played by serotonin in both behavior and cognition, this neurotransmitter system has become a focus of dedicated research efforts to identify novel pathways in Aβ peptide or NFT assembly and/or aggregation (Butzlaff and Ponimaskin, 2016; Schneider et al., 2016; Wirth et al., 2016). Serotonin has been found to increase by 4-fold, respectively in AD raphe cell bodies over controls, while in amygdala synaptic terminals 5-HT was decreased to 0.4-fold in the same AD cases; the accumulation of TPH and its products in the raphe perikarya in AD as the result of diminished transport of TPH to axon terminals and the accumulation of oxidative metabolites of serotonin may contribute to the degeneration of serotonergic neurons in AD (Burke et al., 1990; Wirth et al., 2016). Recent studies have also shown that the administration of selective serotonin reuptake inhibitors (SSRI) to Tg-AD murine models both reduces the production of toxic Aβ peptides and SP formation (Sheline et al., 2014; Butzlaff and Ponimaskin, 2016). For example, SSRI such as the antianxiety/

antidepressant citalopram hydrobromide (Celexa) has been used in AD with varying success while antipsychotics remain the pharmacological agents with most evidence to support their use (Gallagher and Herrmann, 2015). On the other hand other recent investigations, as part of the recent Citalopram for Agitation in Alzheimer Disease (CitAD) study, indicate that higher doses of SSRIs such as citalopram actually may trigger aggression especially in patients with more severe cognitive impairment encountered in the more advanced stages of AD (Schneider et al., 2016).

Genetics of Aggression in Schizophrenia

With a median incidence of 152 cases/M (million) persons (range 77–430 cases/M; c.i. 80%), schizophrenia is a relatively common and perplexing neurological disorder characterized by a series of NPSs that include abnormal psychosocial behavior, anxiety, disorganized thinking and impaired cognition, reduced social engagement and emotional expression, lack of motivation and a significantly increased incidence of aggression (McGrath et al., 2008; Soyka, 2011; Morris et al., 2015; Agarwal et al., 2016; Cocchi et al., 2016; Janoutová et al., 2016; Nowak et al., 2016). Globally, there are an estimated ∼25 million cases of schizophrenia; males are more often affected than females (at a ratio of 1.4 to 1), environmental and lifestyle risk factors include birth in a winter month, at a high latitude, and in an urban setting, and societal problems, such as long-term unemployment, poverty, and homelessness are common (Agarwal et al., 2016; Janoutová et al., 2016; Nowak et al., 2016; van de Leemput et al., 2016). The average life expectancy of people with schizophrenia is ∼10–25 years less than the average, and in the US an estimated 16,000 people die from behaviors related to, or caused by, schizophrenia each year (Agarwal et al., 2016; Janoutová et al., 2016; Nowak et al., 2016; van de Leemput et al., 2016). As with AD, aggressive acts committed by patients with schizophrenia are a major public health concern affecting patients, their families and caregivers as well as organized healthcare and the criminal-justice system. Also similar to AD, schizophrenia appears to target high-level processing functions associated with the neocortex and cortical synaptic connectivity; the genetic contributions to schizophrenia are complex and multifactorial with the integrated contributions of brain genes thought to be centrally involved in auditory processing, altered mood and behavior, anxiety and disorganized thought (Coyle et al., 2016). As previously mentioned, five of these six genes (AR, BDNF, COMT, DBH, NOS1) identified to be dysregulated in this study in AD and aggression have been implicated in the development, onset and/or propagation of schizophrenia. Interestingly both "*dopaminergic and serotoninergic hypotheses for schizophrenia*", involving an elevated genetically-based capacity for striatal increased L-phenylalanine- and/or L-tyrosine-derived DA biosynthesis, altered DA release and defects in the tryptophan-derived serotonin (5-HT) and the serotonin receptor, transporter and synaptic vesicle trafficking systems have been implicated in several of the longest held pathoetiologic- and pathogenic-hypotheses for schizophrenia (Zhang et al., 2014; Baou et al., 2016; Cocchi et al., 2016; Egbujo et al., 2016; Garay et al., 2016; Howes et al., 2017). The overlapping participation of dopaminergic and serotoninergic pathways, especially with DA-metabolizing COMT pathways and serotonin (5-HT) reuptake inhibitors (SSRIs; Zoloft, Paxil, Prozac and other antidepressants) and blockage of serotonin transporter activities are remarkable. The duality of DA and serotonin signaling is further underscored by the actions, for example, of antipsychotic medications such as Brexpiprazole (Rexulti®; Lundbeck, Otsuka Pharmaceutical), a partial agonist at DA D2 and serotonin 5-HT1A receptors and an antagonist at serotonin 5-HT2A receptors, recently approved by the US Food and Drug Administration (US-FDA) for the treatment of acute or advanced cases of schizophrenia (McEvoy and Citrome, 2016). Such dual-action antipsychotic medications have shown positive outcomes, such as the significant reduction of relapse in patients, in two independent Phase 3 randomized controlled clinical trials for schizophrenia, and Phase 3 trials are ongoing in patients with the aggressive behaviors associated with AD (Marder et al., 2016; McEvoy and Citrome, 2016).

Of related interest is the concept of "*retrogenesis*" as it pertains to AD and schizophrenia. Retrogenesis predicts that: (i) brain functions decline in the opposite order to which they develop in humans or during evolution; and that (ii) these anatomical regions of the brain that developed last may be the first to deteriorate with the onset and propagation of NPS illness. Put another way, the expression of genes within anatomical regions known to direct high-level brain processing functions, such as the integration of visual, auditory and other sensory information associated with intellectual abilities, behavior, memory and cognition are: (i) not only especially vulnerable to the pathoetiology and pathobiology of schizophrenia or the AD process; but (ii) are the same brain regions that display a widespread loss of cortical synaptic connectivity driven by multiple risk genes that adversely affect synaptogenesis and synaptic integrity resulting in aggressive behaviors, such as those periodically encountered in AD (Ashford and Bayley, 2013; Douaud et al., 2014; Coyle et al., 2016).

CONCLUSIONS AND SUMMARY

Just as lethargy, inactivity and passivity, and agitation and hyperactivity lie at opposite ends of the NPS spectrum, apathy and aggression lie at opposite ends of NPS behaviors associated with AD. Certain NPSs are central features of both AD and schizophrenia. Once thought to emerge primarily in the later stages of these diseases, NPSs are currently understood to manifest commonly in early disease stages and in prodromal phases such as MCI. Aggression is a common NPS in both MCI and AD, exhibits variability and fluctuation in its presentation during the course of AD, is considerably more prominent in the later stages of AD, is often associated with psychosocial stressors, may be a response to perceived or imagined threats, and requires dutiful intervention when it causes the AD patient to be a threat to their family or care-givers' safety and well-being. Although aggressive behaviors

in AD have received considerable research attention especially over the last 20 years, the molecular-genetic mechanisms involved in both functional and pathological aggression remain incompletely understood and vast gaps in our knowledge remain (Xing et al., 2012; Gallagher and Herrmann, 2015; Smagin et al., 2015). On the other hand, progress is being made on the appreciation that the regulation of complex behaviors such as aggression is controlled by an increasingly defined broad spectrum of highly interactive brain abundant neurotrophins and/or neurotransmitters—these same signaling molecules appear to have both triggering and preventing effects on aggressive behaviors. Similarly, anti-aggression medications: (i) have displayed hypervariable effects on aggressive behaviors in humans and Tg-AD models depending on the medicinal dose, age, gender and disease duration; and (ii) have displayed both inhibitory and stimulating effects on aggressive behaviors, depending largely upon the primary biological receptors where they act and what brain anatomical regions are more exposed to pharmacological treatment (Coyle et al., 2016; McEvoy and Citrome, 2016). Ancillary factors that include diet and other environmental factors, such as level of education, the patient's lifestyle, illicit drug use, ethnicity, the severity and stage of cognitive impairment and inter-current neurological disease have a considerable influence on the degree and extent of NPSs. The interplay of microbial and host genetics and other gene inducing factors are also becoming appreciated as strong contributors to brain gene signaling that strongly impact neurological health and the age-related development of CNS disease (Zhao and Lukiw, 2015).

It is further interesting that the genetic signals associated with AD and aggressive behavior involving the AR, BDNF, COMT, DBH, NOS1 and TPH are all complex multifunctional neurotrophic factors and/or neurotransmitters: (i) that are evolutionarily ancient; and (ii) that can be highly interactive in amplifying or reducing their role in aggressive behaviors from both neuropsychological and interdisciplinary perspectives (Narvaes and Martins de Almeida, 2014; McClam et al., 2015; Coyle et al., 2016). Other factors that can impact the regulation of gene expression including diurnal regulation, oscillatory aspects, stochastic fluctuations of gene expression and their variable transcriptional regulatory roles add further layers of complexity to our understanding of the role of genetics in the aggression associated with AD. It has recently become apparent that biological mechanisms which drive feedforward loops in NPS-relevant gene expression may have strong influence on attenuating the stochasticity of brain gene expression patterns (Barger, 2016; Shearer et al., 2016). The most recent data on the genetics of aggression in AD demonstrate: (i) that both the timescale of selective gene expression; and (ii) fluctuations in the expression of those genes implicated substantially affect the function and performance of biochemical networks, and these factors further influence gene expression plasticity, especially in the transcription-enriched environment of human neurons (**Figure 1**; Barger, 2016; Shearer et al., 2016). It is further interesting that this work is a prime example of a remarkable congruency between GWAS-based and DNA-array and transcriptomic-array-based findings which both show similar fluctuations in the expression of gene families important in both aggression and AD. With certainty: (i) the application of novel comparative gene expression approaches that include observations of temporal changes in the activities of neurotrophic factors and/or neurotransmitters merged with imaging technologies are certain to provide an enduring foundation for the elucidation of what signaling genes in the brain are crucial contributors to complex psychiatric symptoms such as aggression; and (ii) the expression of those NPS-related genes still represent a genuinely perplexing aspect of altered behaviors associated with the AD process. The path to scientific discovery invariably originates from an awareness of what is unknown. What we do know for certain is that the genetics of AD and aggression are characterized by prominent intrinsic variabilities in the highly interactive expression of genes that are complex, dynamic and evolving, and this knowledge is sure to help guide and shape the future direction of both neurotherapeutics and NPS research.

AUTHOR CONTRIBUTIONS

WJL and the late James M. Hill collected and categorized all brain sample extracts, performed all experiments and wrote the article; EIR performed statistical and bioinformatics analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00087/full#supplementary-material

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The Relationship between Cerebral Small Vessel Disease, Hippocampal Volume and Cognitive Functioning in Patients with COPD: An MRI Study

Fiona A. H. M. Cleutjens[1], Rudolf W. H. M. Ponds[2], Martijn A. Spruit[1,3], Saartje Burgmans[4], Heidi I. L. Jacobs[4], Ed H. B. M. Gronenschild[4], Julie Staals[5], Frits M. E. Franssen[1], Jeanette B. Dijkstra[2], Lowie E. G. W. Vanfleteren[1], Paul A. Hofman[6], Emiel F. M. Wouters[1,7] and Daisy J. A. Janssen[1]*

[1]Department of Research and Education, Centre of Expertise for Chronic Organ Failure (CIRO), Horn, Netherlands, [2]Department of Medical Psychology, Maastricht UMC+/School for Mental Health and Neurosciences (MHeNS), Maastricht, Netherlands, [3]Department of Respiratory Medicine, Maastricht University Medical Centre, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht, Netherlands, [4]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Centre Limburg, Maastricht University, Maastricht, Netherlands, [5]Department of Neurology, Maastricht University Medical Centre, Maastricht, Netherlands, [6]Department of Radiology, Maastricht University Medical Centre, Maastricht, Netherlands, [7]Department of Respiratory Medicine, Maastricht UMC+, Maastricht, Netherlands

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***Correspondence:**
Fiona A. H. M. Cleutjens
fionacleutjens@ciro-horn.nl

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The neural correlates of cognitive impairment in chronic obstructive pulmonary disease (COPD) are not yet understood. Structural brain abnormalities could possibly be associated with the presence of cognitive impairment through cigarette smoke, inflammation, vascular disease, or hypoxemia in these patients. This study aimed to investigate whether macrostructural brain magnetic resonance imaging (MRI) features of cerebral small vessel disease (SVD) and hippocampal volume (HCV) are related to cognitive performance in patients with COPD. A subgroup of cognitively high and low-performing COPD patients of the COgnitive-PD study, underwent a brain 3T MRI. SVD as a marker of vascular damage was assessed using qualitative visual rating scales. HCV as a marker of neurodegeneration was assessed using the learning embedding for atlas propagation (LEAP) method. Features of SVD and HCV were compared between cognitively high and low-performing individuals using Mann Whitney U tests and independent samples *t*-tests, respectively. No group differences were reported between 25 high-performing (mean age 60.3 (standard deviation [SD] 9.7) years; 40.0% men; forced expiratory volume in first second [FEV_1] 50.1% predicted) and 30 low-performing patients with COPD (mean age 60.6 (SD 6.8) years; 53.3% men; FEV_1 55.6% predicted) regarding demographics, clinical characteristics, comorbidities and the presence of the SVD features and HCV. *To conclude*, the current study does not provide evidence for a relationship between cerebral SVD and HCV and cognitive functioning in patients with COPD. Additional studies will be needed to determine other possible mechanisms of cognitive impairment in patients with COPD, including microstructural brain changes and inflammatory-, hormonal-, metabolic- and (epi)genetic factors.

Keywords: cerebral small vessel diseases, chronic obstructive pulmonary disease, cognition, hippocampus, magnetic resonance imaging

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic disease which is primarily characterized by progressive airflow limitation (Vestbo et al., 2013). Beyond respiratory impairment, patients with COPD often suffer from a variety of comorbid and biological conditions (Divo et al., 2012; Vanfleteren et al., 2013). These biological changes may have adverse effects on the brain leading to cognitive impairment. General cognitive impairment is four times more likely to occur in patients with COPD than in non-COPD controls and involves several cognitive domains, such as psychomotor speed, planning, memory and cognitive flexibility (Cleutjens et al., 2017). Impairments in working and verbal memory have been found in one out of three patients with COPD (Cleutjens et al., 2017). Although the pathogenesis of cognitive impairment in COPD has been searched in oxidative stress, hypoxemia, systemic inflammation and comorbidities, the exact pathways remain unknown (Dodd et al., 2010; Cleutjens et al., 2014a; Lahousse et al., 2015). Structural brain abnormalities are considered an important cause of cognitive impairment, especially decreased hippocampal volume (HCV), which has been associated with decreased memory (Soininen et al., 1994; Schuff et al., 2009; Wolz et al., 2010b), and features of cerebral small vessel disease (SVD; Cai et al., 2015). SVD refers to pathological processes affecting the small arteries, arterioles, venules and capillaries of the brain. For example, chronic hypoperfusion can occur, whereby the supply of oxygen and nutrients to the brain tissue is slowly cut (Cai et al., 2015). Hypoxemia is thought to act in an additive manner in the development of structural brain abnormalities (Miyamoto and Auer, 2000). Structural brain abnormalities associated with SVD can be seen on magnetic resonance imaging (MRI) as white matter hyperintensities (WMHs), lacunes, cerebral microbleeds and perivascular spaces (PVS). The main risk factors for SVD are increased age and hypertension.

In comparison to control participants, COPD patients showed smaller HCV (Li and Fei, 2013), reduced white matter integrity and regional gray matter density (Dodd et al., 2012; Zhang et al., 2012), periventricular white matter lesions (van Dijk et al., 2004), disturbed functional activation of gray matter (Dodd et al., 2012), and a higher prevalence of cerebral microbleeds (Lahousse et al., 2013). Possible mechanisms, common in COPD, which may contribute to brain abnormalities and cognitive impairment are cigarette smoke, inflammation, vascular disease and hypoxemia (Dodd et al., 2010). Yet, the relationship between structural brain abnormalities, especially HCV and features of SVD and cognitive functioning in COPD remains unexplored.

In order to verify whether SVD and HCV may explain the level of cognitive functioning in patients with COPD, this study aimed to assess whether and to what extent SVD and HCV differ between COPD patients with high and low cognitive performance. *A priori*, we hypothesized that COPD patients with low cognitive performances are characterized by a higher SVD load, and smaller HCV compared to COPD patients with high cognitive performances.

MATERIALS AND METHODS

Design

This cross sectional study is part of a longitudinal study (COgnitive-PD study) aimed at mapping and understanding neuropsychological functioning in patients with COPD. Details of the methodology of this study and data concerning cognition have been described before (Cleutjens et al., 2014b, 2017).

Study Population

For this study, we selected the first 30 cognitively low-performing and the first 25 high-performing patients with COPD during inclusion of the COgnitive-PD study (n = 183) who were willing to undergo brain MRI. Six core tests of the detailed neuropsychological test battery from the Cognitive-PD study (**Table 1**) were used to distinguish cognitively high-performing individuals from low-performing individuals (Burgmans et al., 2009; for details about the tests, please see the Cognitive-PD study protocol (Cleutjens et al., 2014b)). In addition to the exclusion criteria of the COgnitive-PD study (Cleutjens et al., 2014b), patients were not eligible if they had contraindications to undergo a brain MRI (claustrophobia, a cardiac pacemaker, a cochlear implant, a neurostimulator, or other metal implants in the body). The study was approved by the Medical Ethics Committee of the Maastricht University Medical Centre (NL45127.068.13). All patients provided written informed consent to participate in the study.

Brain MRI Acquisition

Patients had brain MRI on a research-dedicated 3-T MRI scanner (Siemens, Netherlands) operated by research-dedicated technical staff in the Maastricht University Medical Center. Sequences included T1-weighted sagittal sequence (TR = 8.14 ms, TE = 3.72 ms, FA = 8°, FOV = 256 × 256 × 155 mm, acquisition matrix = 256 × 256, number of slices = 155, voxel size = 1.00 mm isotropic), T2-weighted transversal sequence (TR = 3000 ms, TE = 80 ms, FA = 90°, FOV = 230 × 230 × 154 mm, acquisition matrix = 512 × 512, number of slices = 28, slice gap = 0.50 mm, voxel size = 0.45 × 0.45 × 5.5 mm), fluid-attenuated inversion recovery (FLAIR) sagittal sequence (TR = 4800 ms, TE = 275 ms, TI = 1650 ms, FOV = 250 × 250 × 154 mm, acquisition matrix = 240 × 240, number of slices = 275, slice gap = 0.56 mm, voxel size = 1.04 × 1.04 × 0.56 mm), and T2*-weighted transversal sequence (TR = 844 ms, TE = 16 ms, FA = 18°, FOV = 230 × 230 × 154 mm, acquisition matrix = 512 × 512, number of slices = 28, slice gap = 0.50 mm, voxel size = 0.45 × 0.45 × 5.5 mm).

MRI Analysis

All MRIs were analyzed blinded to patient's cognitive status. WMHs (**Figure 1A**) were classified as periventricular WMHs (PVWMHs; localized around the lateral ventricles) or deep WMHs (DWMHs; localized within the deep WM) on the Fazekas scale ranging from 0 to 3, using FLAIR and T2-weighted images (Fazekas et al., 1987). Additionally, the age-related

TABLE 1 | Cognitive performance per core subtest on the COgnitive-PD study neuropsychological test battery.

	High-performing COPD patients (n = 25)		Low-performing COPD patients (n = 30)	
Outcome measure	**Mean (SD)**	**$Z \leq -1$**	**Mean (SD)**	**$Z \leq -1$**
VVLT total recall (number correct: 0–75)*	54.4 (8.6)	0.0%	35.4 (9.1)	50.0%
VVLT delayed recall (number correct: 0–15)*	11.3 (2.8)	4.0%	6.3 (2.8)	56.7%
GIT-II animal naming (number of animal names)‡	25.5 (5.1)	0.0%	19.2 (5.6)	30.0%
LDST 60 s written (number correct: 0–125)*§	33.8 (6.1)	0.0%	23.4 (6.1)	50.0%
CST-C (time in seconds)†	32.1 (11.0)	4.0%	50.1 (18.0)	36.7%
SCWT card III (time in seconds)†	46.7 (43.4)	16.0%	63.3 (21.9)	80.0%

*Abbreviations: CST, Concept Shifting Test; GIT, Groningen Intelligence Test; LDST, Letter Digit Substitution Test; SD, standard deviation; SCWT, Stroop Colour-Word Test; VVLT, Visual Verbal Learning Test; $Z \leq -1$, percentage of patients with a Z score of −1 or lower. *Higher scores indicate better performance; ‡Indicates score has no upper limit; §At least one of out the two LDST 60 subtests had to be scored with a score less than 1.0 SD below the age-, gender- and education-specific mean of the MAAS study population to have an impaired score on the LDST subtest; †Higher scores indicate worse performance.*

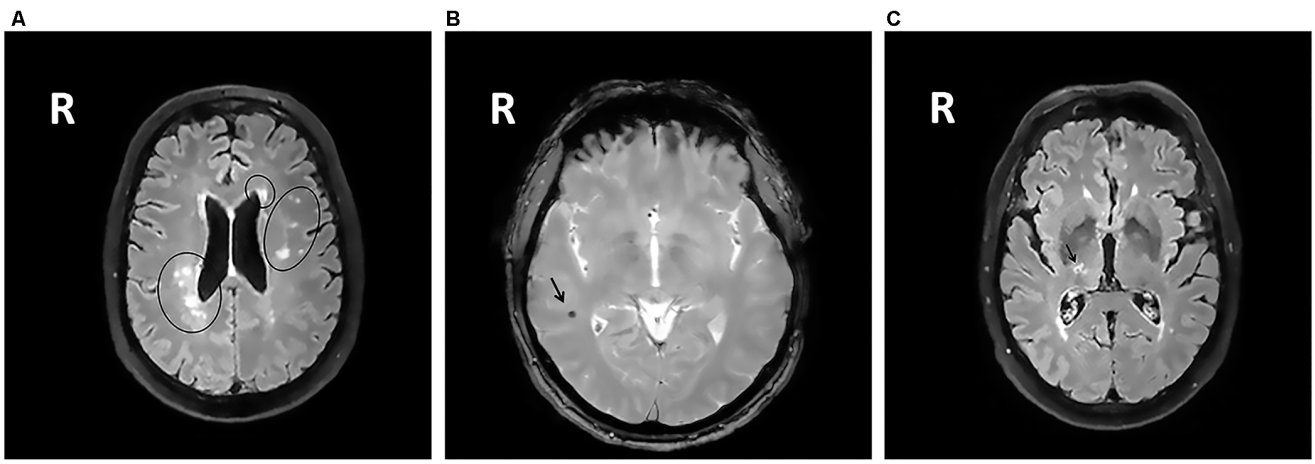

FIGURE 1 | (A) Fluid-attenuated inversion recovery (FLAIR) brain magnetic resonance imaging (MRI) scan showing periventricular WMHs and deep WMHs (DWMHs) in both hemispheres. WMH, white matter hyperintensities; R, right. **(B)** T2*-weighted brain MRI scan showing a microbleed located within the right white matter. R, right. **(C)** FLAIR brain MRI scan showing a lacune located in the deep gray matter. R, right.

white matter changes (ARWMC) scale was applied to rate WMHs more specifically per brain region (Wahlund et al., 2001). PVS (**Figure 2**) were defined as small, linear or pointy structures of cerebrospinal fluid intensity measuring <3 mm in size and following the course of the vessels, at the level of the basal ganglia and in the centrum semiovale. T2-weighted images were used in order to rate PVS on a qualitative scale (Potter et al., 2015). Microbleeds (**Figure 1B**) and lacunes (**Figure 1C**) were rated using T2*, T2 and FLAIR images. Microbleeds were defined as small (<5 mm), homogeneous, round foci of low signal intensity on T2* in the cerebellum, brainstem, basal ganglia, white matter, or cortico-subcortical junction, differentiated from vessel flow voids and mineral depositions in the globi pallidi (Wardlaw et al., 2013a). Lacunes were defined as rounded or ovoid lesions with diameters from 3 mm to 20 mm located in the basal ganglia, internal capsule, centrum semiovale, or brainstem and carefully distinguished from WMH and PVS (Wardlaw et al., 2013b). An SVD compound score, expressing the level of cerebral SVD load, was calculated according to the method of Staals et al. (2014) WMHs and PVS were rated by two trained raters. In a random sample of one third of the brain scans, the agreement between raters was high with intraclass correlation coefficient (ICC) greater than 0.80 for the Fazekas scale (both PVWMH and DWMH); ICC greater than 0.75 for the ARWMC except for the basal ganglia and the infratentorial area; ICC greater than 0.80 regarding PVS in the basal ganglia and greater than 0.65 in the centrum semiovale. Microbleeds and lacunes, were rated by an experienced neurologist (JS). Since one single MRI scanner performed all measurements no intervariability study was performed. HCV was measured on T1-weighted images using the Learning Embeddings Atlas Propagation (LEAP) method (Wolz et al., 2010a). HCV was normalized by multiplying the native space volume with the affine scaling factor (ASF), also derived with LEAP. An ASF value of >1 indicated expansion and a value <1 contraction required to register each individual's brain to the atlas template (Buckner et al., 2004). LEAP data were provided by Wolz (Ixico Ltd. and Imperial College, London).

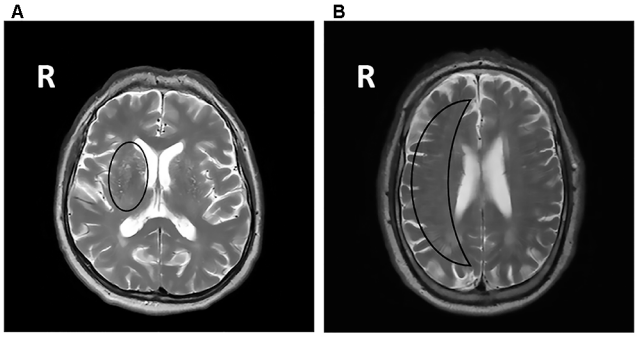

FIGURE 2 | T2-weighted brain MRI scans showing symmetric extensive PVS at the level of the basal ganglia (A) and in the centrum semiovale **(B)**. PVS, perivascular spaces; R, right.

Other Measures

Age, gender, educational level (according to The Dutch Standard Classification of Education (C.B.S., 2001)), marital status, visual and hearing impairment, handedness, smoking behavior and self-reported hypertension and comorbidities (Charlson Comorbidity Index (Charlson et al., 1987)) were recorded. Moreover, data on body mass index (BMI), long-term oxygen therapy, modified Medical Research Council (mMRC) dyspnea scale (American Thoracic Society, 1982), post-bronchodilator spirometry (forced vital capacity (FVC), FVC% predicted, forced expiratory volume in the first second (FEV_1), FEV_1% predicted and FEV_1/FVC), resting arterial blood gases (arterial oxygen partial pressure [PaO_2], arterial partial pressure of carbon dioxide [$PaCO_2$] and oxygen saturation [SaO_2]), and single breath carbon monoxide diffusing capacity (DLCO% predicted) were collected.

Statistical Analyses

All statistical analyses were done using SPSS 21.0 (SPSS Inc. Chicago, IL, USA). A p-value < 0.05 was considered as statistically significant. Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean and standard deviation (SD) or median and interquartile range (IQR).

Raw test scores on the neuropsychological test battery were transformed into age, gender and education corrected Z-scores based on normative data from the Maastricht Aging Study (MAAS). Cognitively low-performing individuals had a score less than 1.0 SD below the age-, gender- and education-specific mean of the MAAS study population for at least two core tests and high-performing individuals had a score more than 1.0 SD above the age-, gender- and education-specific mean of the MAAS study population for at least two core tests (**Table 1**; Singh et al., 2013).

Patient characteristics were compared between the groups using Chi-square tests for categorical variables and independent samples t-test or Mann-Whitney U test, as appropriate for continuous variables. Mann Whitney U tests were performed in order to compare high and low-performing individuals based on features of SVD. HCV were compared using independent samples t-tests. The p-values were adjusted using the Benjamini-Hochberg correction (Benjamini and Hochberg, 1995) for multiple tests, with a false discovery rate of 5%.

RESULTS

Patient Characteristics

Cognitively low-performing patients had significantly worse mean scores on all core tests of the COgnitive-PD test battery compared to high-performing patients (**Table 1**). Demographic and clinical characteristics, including smoking behavior, FEV_1, arterial blood gases and diffusion capacity were comparable between cognitively high and low-performing patients. The groups did not differ on reported comorbidities (**Table 2**).

Structural Brain Abnormalities in High and Low-Performing Patients with COPD

No differences were seen on the DWMH and PVWMH Fazekas subscales (**Table 3**). WMHs mapped specifically per brain region did not differ between low and high-performing patients. PVS in basal ganglia or centrum semiovale did not differ between the groups. There was no difference in presence of lacunes or microbleeds. The level of cereberal SVD load was comparable between the two groups. No significant difference was found between low and high-performing individuals regarding the left and right HCV (**Table 3**).

DISCUSSION

Key Findings

The goal of the current brain MRI study was to assess whether differences in SVD features and/or HCV are related to the level of cognitive functioning in patients with COPD. In contrast to our hypothesis that COPD patients with low cognitive performances are characterized by a higher SVD load, and smaller HCV compared to COPD patients with high cognitive performances, we found that structural brain changes were comparable between COPD patients with low or high cognitively performance.

We did not find a difference in the compound score of SVD between high and low-performing COPD patients. Indeed, SVD may also be found in individuals with normal cognitive performance (Duning et al., 2005) and the exact pathophysiological link between SVD features and cognitive impairment remains not completely understood. It is suggested that individuals with normal cognitive performance have a greater cognitive reserve by which they are able to compensate certain brain pathologies better than others (Stern et al., 2005). However, the low and high-performing groups in our study were comparable for educational level, which is considered to be one on of the best indicators for cognitive reserve. Although not significant, we observed a trend towards more hypertension, one of the main risk factors for SVD (Pantoni and Garcia, 1997), in cognitively low-performing patients. 34.5% of patients without physician-diagnosed hypertension had an elevated systolic blood

TABLE 2 | Characteristics of the study population.

Characteristic	High-performing COPD patients (n = 25)	Low-performing COPD patients (n = 30)	Benjamini-Hochberg P-value
Demographics			
Age, years	60.3 (9.7)	60.6 (6.8)	0.941
Male, *n* (%)	10 (40.0)	16 (53.3)	0.497
Lower education, *n* (%)	8 (32.0)	7 (23.3)	0.476
Exacerbation history in the previous 12 months			
0–1 exacerbations, *n* (%)	10 (40.0)	10 (33.3)	0.408
2 ≥ exacerbations, *n* (%)	15 (60.0)	20 (66.7)	
Health condition			
Visual impairment, *n* (%)	4 (16.0)	7 (23.3)	0.524
Hearing impairment, *n* (%)	6 (24.0)	6 (20.0)	0.612
BMI (kg/m^2), mean, (SD)	25.1 (5.2)	27.5 (7.7)	0.458
Oxygen therapy, *n* (%)	6 (24.0)	3 (10.0)	0.458
mMRC (grade), mean (SD)	2.1 (2.0)	2.6 (2.0)	0.458
Smoking behavior			
Current smoker, *n* (%)	3 (12.0)	7 (23.3)	0.458
Former smoker, *n* (%)	20 (80.0)	23 (76.7)	
Never smoker, *n* (%)	2 (8.0)	0 (0.0)	
Spirometry and arterial blood gases			
FEV_1/FVC, mean (SD)	37.7 (13.5)	47.0 (14.6)	0.272
FEV_1 (% predicted), mean (SD)	50.1 (20.1)	55.6 (20.0)	0.497
SaO_2 (%), mean (SD)	93.7 (2.7)*	94.0 (2.6)	0.844
SaO_2 before 6MWT (%), mean (SD)	94.5 (2.5)	94.3 (2.1)	0.771
		88.3 (6.5)	
SaO_2 after 6MWT (%), mean (SD)	87.8 (7.1)	9.6 (1.5)	0.770
	9.3 (1.4)*		
PaO_2 (kPa), mean (SD)	9.3 (1.1)‡	9.7 (1.6)§	0.458
			0.361
PaO_2 off-oxygen (kPa), mean (SD)	5.8 (1.8)*	6.4 (2.2)	
$PaCO_2$ (kPa), mean (SD)	5.8 (2.0)‡	6.2 (2.1)§	0.497
		49.6 (17.4)	0.534
$PaCO_2$ off-oxygen (kPa), mean (SD)	49.7 (18.6)*		
DLCO (% predicted), mean (SD)			0.988
Comorbidities			
Charlson comorbidity index score, mean, (SD)	2.6 (1.6)	3.5 (2.0)	0.425
Myocardial infarction, *n* (%)	2 (8.0)	10 (33.3)	0.272
Congestive heart failure, *n* (%)	2 (8.0)	5 (16.7)	0.497
Peripheral vascular disease, *n* (%)	4 (16.0)	9 (30.0)	0.458
Cerebrovascular disease, *n* (%)	3 (12.0)	6 (20.0)	0.497
Connective tissue disease, *n* (%)	6 (24.0)	8 (26.7)	0.631
Peptic ulcer disease, *n* (%)	4 (16.0)	4 (13.3)	0.631
Mild, moderate or severe liver disease, *n* (%)	2 (8.0)	0 (0.0)	0.458
Diabetes mellitus, *n* (%)	3 (12.0)	8 (26.7)	0.458
Hemiplegia, *n* (%)	2 (8.0)	2 (6.7)	0.705
Moderate to severe chronic kidney disease, *n* (%)	1 (4.0)	1 (3.3)	0.775
Solid or malignant tumors, *n* (%)	3 (12.0)	6 (20.0)	0.497
Obstructive sleep apnea, *n* (%)	3 (12.0)	7 (23.3)	0.476
Hypertension, *n* (%)	2 (8.0)	11 (36.7)	0.272
HADS anxiety score	6.9 (4.7)	9.1 (4.2)	0.425
HADS anxiety >10 points, *n* (%)	5 (20.0)	11 (36.7)	0.458
HADS depression score (points)	7.0 (4.6)	7.9 (3.5)	0.553
HADS depression >10 points, *n* (%)	5 (20.0)	8 (26.7)	0.523

*Abbreviations: 6MWT, six-minute walking test; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; FEV_1/FVC, Tiffeneau index; HADS, Hospital Anxiety Depression Scale; IQR, interquartile range; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial oxygen partial pressure; SaO_2, oxygen saturation; SD, standard deviation. *n = 24; ‡n = 18; §n = 27.*

pressure (≥140) or elevated diastolic blood pressure of ≥90. Yet, the percentage of patients with elevated systolic or diastolic blood pressure did not differ between the low and high-performing group.

When we mapped WMHs specifically per brain region, these structural brain abnormalities were not able to differentiate both groups. A population-based study reported that COPD patients had more severe PVWMHs than persons without COPD (van Dijk et al., 2004). Characteristics of the control group were not reported. Our results show no difference in DWMHs between low and high-performing patients. Contradictory findings on the differential impact of PVWMHs

TABLE 3 | SVD and (normalized) hippocampal volume.

		High-performing COPD patients (*n* = 25)	Low-performing COPD patients (*n* = 30)	Benjamini-Hochberg *P*-value
SVD				
WMH Fazekas scale				
PVH, median (IQR)		1.0 (0.0–1.5)	1.0 (0.0–2.0)	0.509
DWMH, median (IQR)		1.0 (1.0–1.0)	1.0 (1.0–2.0)	0.329
WMH ARWMC total, median (IQR)		4.0 (4.0–6.0)	6.0 (3.8–10.0)	0.329
Frontal, median (IQR)	Left	1.0 (0.5–1.0)	1.0 (1.0–1.0)	0.329
	Right	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.702
Parietal occipital, median (IQR)	Left	1.0 (0.5–1.0)	1.0 (1.0–2.0)	0.329
	Right	1.0 (1.0–1.0)	1.0 (1.0–2.0)	0.386
Temporal, median (IQR)	Left	0.0 (0.0–0.5)	0.0 (0.0–1.0)	0.329
	Right	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.509
Basal ganglia, median (IQR)	Left	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.643
	Right	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.509
Infratentorial, median (IQR)	Left	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.329
	Right	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.329
PVS				
Basal ganglia, median (IQR)		0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.985
Centrum semiovale, median (IQR)		1.0 (0.0–1.0)	1.0 (0.0–2.0)	0.329
Lacunes, *n* (%)		5 (20.0)	5 (17.0)	0.792
Microbleeds, *n* (%)		2 (8.0)	1 (3.3)	0.603
Total SVD score, median (IQR)		1.0 (0.0–2.0)	0.0 (0.0–2.0)	0.761
Hippocampal volume				
Left HCV (mm^3), mean (SD)		2813.7 (328.1)	2648.8 (328.2)	0.329
Right HCV (mm^3), mean (SD)		2834.3 (264.6)	2751.2 (243.0)	0.418

Abbreviations: ARWMC, the age-related white matter changes scale; COPD, chronic obstructive pulmonary disease; DWMH, deep white matter hyperintensity; HCV, hippocampal volume; PVS, enlarged perivascular spaces; IQR, interquartile range; PVH, periventricular hyperintensity; SD, standard deviation; SVD, small vessel disease.

and DWMHs on cognition exist, probably due to varying terminology and definitions for PVWMHs and DWMHs (Kim et al., 2008). Soriano-Raya et al. (2012) suggested that only DWMHs, not PVWMHs, are related to cognitive impairments in middle-aged individuals. De Groot et al. (2000) showed that PVWMHs are associated with cognition and DWMHs with depression. High and low cognitively performing COPD patients did not differ on symptoms of depression.

Van Dijk et al. (2004) did not find an association between COPD and lacunes. In addition, our study showed no difference in the incidence of lacunes between high and low-performing COPD patients. In a large population-based study, a higher prevalence of cerebral microbleeds was associated with COPD (Lahousse et al., 2013). Our study did not find differences in the presence of microbleeds between high and low-performing COPD patients. It might be that patients with COPD are at risk for microbleeds due to comorbid processes, such as systemic inflammation (Maclay and MacNee, 2013) without specific cognitive consequences.

Finally, no differences in the extent of PVS were found between high and low-performing patients. The exact causes of PVS are uncertain but abnormalities at the blood brain interface and inflammation have been associated with PVS (Wuerfel et al., 2008; Wardlaw et al., 2009). Studies suggest that smoking and reduced lung function cause inflammation and that both variables might act in an additive manner (Gan et al., 2005; Pelegrino et al., 2013). Our groups were comparable for lung function and smoking status which might explain the absence of differences in the extent of PVS.

MRI markers of SVD including WMHs, lacunes and microbleeds have been related to cognitive performance in population-based (Prins et al., 2005) and stroke cohorts (Gregoire et al., 2011; Patel et al., 2013). Yet, effect sizes have been small across studies (van der Vlies et al., 2012; Kloppenborg et al., 2014). The relatively weak or inconsistent correlations may be explained by the fact that it is not the individual lesions that determine the impact on cognitive performance, but the cumulative effect of these small, spatially distributed lesions. This is in line with findings of Schneider et al. (2007) who demonstrated multiple brain pathologies in cases with dementia using autopsy.

Rates of hippocampal atrophy are sensitive features of neurodegeneration. In normal aging (Ystad et al., 2009) and in several neurological disorders, including AD (Laakso et al., 1995), temporal lobe epilepsy (Kilpatrick et al., 1997), and depressed elderly (Steffens et al., 2011), measurements of volumes of the hippocampus already have been shown to be positively correlated with impaired performances on neuropsychological tests, especially in the memory domain. Also in COPD, HCV may be a proximity marker for cognitive (memory) impairment. Yet, no differences were observed in left and right HCV between cognitively low and high-performing COPD patients. Indeed, compared to cross-sectional studies, effect sizes are stronger across longitudinal studies (Raz et al., 2007).

Alternate mechanisms than structural brain abnormalities may explain cognitive performances are probably multifactorial. First, worse cognitive performance in the low-performing COPD group might be explained by damage caused by oxidative stress,

like oxidized proteins, glycated products and lipid peroxidation which lead to degeneration of neurons and impairments in cognitive functioning (Popa-Wagner et al., 2013). Second, although not significant, the high-performing group more often received supplemental oxygen. Regular use of supplemental oxygen therapy has been shown to decrease the risk for cognitive impairment in patients with COPD (Thakur et al., 2010). Third, it is possible that the low-performing group had more comorbidities associated with cognition, other than mentioned in the Charlson comorbidity index (e.g., osteoporosis and Major Depressive Disorder) compared to the high-performing group. Fourth, mitochondrial dysfunction in COPD affects tissues with high energetic demands such as skeletal muscle, cardiac muscle and the central nervous system accompanied by cognitive deficits (Mancuso et al., 2009).

Limitations

Although we used a 3-T MRI scanner, the prevalence of detected SVD features was rather low. Furthermore, the number of patients investigated in this study was small and therefore we might have a low power to detect group differences in the outcome of interest. However, the group was relatively homogeneous with regard to demographical and clinical characteristics. Nevertheless, selection bias cannot be excluded, because, for instance, patients with personal interest are more willing to participate. We used visual rating scales, and although validated, these have some limitations, such as non-linearity of data, lack of sensitivity to small changes, and subjective assessment. By using non-parametric tests and calculating an ICC, we tried to compensate for these limitations. Moreover, Z scores below −1.0 SD and above +1 SD were considered as low and high cognitive performance, respectively. These score cutoff scores may not have been able to differentiate both groups sufficiently. Yet, Singh et al. (2013) considered a Z scores below −1.0 SD as being impaired in a COPD population. Though not the goal of this study, future inclusion of a control group could provide more insight into COPD specifica brain-cognition correlations. Additionally, this cross-sectional study can only determine associations, no causal relationships nor the sequence of the development of cognitive impairment. Therefore, future studies should assess cognitive impairment at various stages of the disease, taking into account varying degrees of hypoxemia.

Conclusions

Using macrostructural MRI features of SVD and HCV, we found no differences between cognitively low and high-performing patients with COPD. This suggests that SVD and HCV are not related to cognitive performance in patients with COPD. Additional studies will be needed to get a better understanding of the mechanisms leading to cognitive impairment in COPD patients, including inflammatory factors, hormonal responses, metabolic disturbances, (epi)genetic or lifestyle factors, or microstructural brain changes using Diffusion Tensor Imaging.

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FAHMC, RWHMP, MAS, SB, HILJ, EHBMG, JS, FMEF, JBD, LEGWV, PAH, EFMW and DJAJ: substantial contributions to the conception or design of the work, and/or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published.

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frontiers in Aging Neuroscience

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Personality, Cortisol, and Cognition in Non-demented Elderly Subjects: Results from a Population-Based Study

*Sami Ouanes[1], Enrique Castelao[1], Armin von Gunten[1], Pedro M. Vidal[2], Martin Preisig[1] and Julius Popp[1]**

[1] Department of Psychiatry, University Hospital of Lausanne, Lausanne, Switzerland, [2] Department of Internal Medicine, University Hospital of Lausanne, Lausanne, Switzerland

Certain personality traits, in particular higher neuroticism, have been associated, on one hand, with elevated cortisol levels, and on the other hand, with poorer cognitive performance. At the same time, several studies highlighted the association between high cortisol and poor cognitive functioning. Here, we hypothesized that increased cortisol may be associated with poorer cognition and with certain personality traits (mainly high neuroticism), and that personality might explain the association between cortisol and cognition. A cross-sectional analysis was conducted using data from Colaus/PsyColaus, a population-based study involving residents of Lausanne, Switzerland. Salivary cortisol samples (upon waking, 30 min after waking, at 11 am and at 8 pm) along with cognitive and personality measures were obtained from 643 non-demented participants aged at least 65. Personality traits were assessed using the NEO Five-Factor Inventory (NEO-FFI). We examined the links between the cortisol Area under the Curve (AUC), the Clinical Dementia Rating Sum of Boxes (CDRSOB) and the NEO-FFI scores. No association was found between personality traits and the CDRSOB or the MMSE score, controlling for age, sex, depression, education and BMI. However, the executive functioning domain *z*-score was negatively associated with agreeableness ($p = 0.005$; slope $= -0.107$ [-0.181; -0.033]) and openness ($p = 0.029$; slope $= -0.081$ [-0.154; -0.008]) after controlling for age, sex, depression, education and BMI. The CDRSOB score was positively associated with the cortisol AUC after controlling for age, sex, BMI, education and depression, ($p = 0.003$; slope $= 0.686$ [0.240; 1.333]). This association remained significant after controlling for personality traits and for the interaction between personality traits and the cortisol AUC ($p = 0.006$; slope $= 0.792$ [0.233; 1.352]. High agreeableness and openness might be associated with poorer executive performance in later life. Increased cortisol may be associated with both specific personality traits (high extraversion, low openness) and worse cognitive performance. Increased salivary cortisol does not mediate the relationship between personality traits and cognitive impairment.

Keywords: cognition, personality, cortisol, memory, dementia, neuroticism, agreeableness, openness

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Xiao Zhen Lv, Peking University, China

****Correspondence:***
Julius Popp
julius.popp@chuv.ch

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INTRODUCTION

Certain personality traits (in particular neuroticism and to a lesser extent extraversion and openness) have been associated with Hypothalamus-Pituitary-Adrenal (HPA) axis dysregulation. Indeed, people with higher neuroticism tend to exhibit greater emotional responses to psychosocial stressors (Garcia-Banda et al., 2014). They also tend to have higher cortisol levels, likely reflecting a more pronounced stimulation of the HPA axis by psychosocial stressors (Portella et al., 2005; Yoshino et al., 2005; Gerritsen et al., 2009; Nater et al., 2010; Garcia-Banda et al., 2014; Miller et al., 2016).

However, other studies did not replicate this finding (Adler et al., 1997; Schommer et al., 1999; Ferguson, 2008) and some even reported a negative association between cortisol and neuroticism (Ballenger et al., 1983; LeBlanc and Ducharme, 2005).

Extraversion has also been associated with elevated cortisol plasma levels (Miller et al., 1999; LeBlanc and Ducharme, 2005), while agreeableness has been associated with lower salivary cortisol levels (Parent-Lamarche and Marchand, 2015).

Elevated cortisol levels have been associated with poorer cognitive performance in non-demented subjects (Lupien et al., 1994; Lee et al., 2008; Popp et al., 2009; Geerlings et al., 2015) as well as with more rapid disease progression in patients with Mild Cognitive Impairment (MCI) linked to Alzheimer's Disease (AD) (Csernansky et al., 2006; Popp et al., 2015).

Furthermore, some personality traits have been associated with poorer cognitive performance and even with an increased risk of dementia (von Gunten et al., 2009). Indeed, in older individuals, higher neuroticism has been associated with poorer cognitive performance independently of depression (Boyle et al., 2010), and in particular with poorer episodic memory (Wilson et al., 2004). High neuroticism and low conscientiousness were associated with greater decline in executive functions (Caselli et al., 2016). In a meta-analysis examining the link between specific facets of personality and the risk of AD, individuals in the top quartile of neuroticism or the lowest quartile of conscientiousness had a threefold increased risk of incident AD (Terracciano et al., 2014).

Furthermore, previous studies examined the link between personality traits and either the HPA axis or the cognitive performance. As far as we know, no previous study scrutinized the inter-relationships between personality traits, the HPA axis and cognition.

In the light of these results highlighting that certain personality traits (higher neuroticism, in particular) might be associated with increased cortisol, that high cortisol might have deleterious cognitive effects, and that some personality traits might be associated with poorer cognition and increased risk for dementia, we hypothesized that personality traits might mediate the link between cortisol levels and cognitive impairment, in particular in episodic memory and executive functions.

MATERIALS AND METHODS

Participants

A cross-sectional analysis was conducted using data from the first follow-up of the longitudinal population-based CoLaus/PsyCoLaus study. The methodological features of this study were already described in detail (Firmann et al., 2008; Preisig et al., 2009). CoLaus/PsyColaus included a random sample of 6734 subjects (age range: 35–75 years) selected from the residents of the city of Lausanne, Switzerland, between 2003 and 2007. All subjects were invited to participate at the first follow-up, which took place between 2009 and 2013. A total of 4004 subjects accepted these new physical and psychiatric evaluations which also included salivary cortisol measures. In addition, all subjects aged 65 or older ($n = 1918$) were invited to undergo a neuropsychological assessment. Information on demographic, medical, and treatment history as well as smoking and alcohol consumption was gathered using semi-structured interviews conducted by trained interviewers or self-rating questionnaires. Psychiatric/behavioral disorders were assessed using the Diagnostic Interview for Genetic Studies (DIGS) (Preisig et al., 1999). Cardio-metabolic disorders were assessed clinically and with the use of biochemical measures. The distribution of age groups, sex and geographic distributions in CoLaus/Psycholaus participants at baseline were similar to the source population (Firmann et al., 2008).

Cognitive Assessment

A neuropsychological and clinical examination as well as an assessment of the participants' daily living activities were performed by trained master-level psychologists blinded for the salivary cortisol levels.

The neuropsychological assessment included:

- The assessment of the global cognitive performance using the Mini Mental State Examination (MMSE) (Folstein et al., 1975), the most commonly used screening tool for global cognitive impairment. MMSE scores range from 0 to 30, a higher score indicating better performance.
- The assessment of *memory* using the Grober and Buschke Double Memory Test (DMT) (Buschke et al., 1997).
- The assessment of *verbal fluency* using the DO40 picture-naming test (Deloche and Hannequin, 1997), the letter (phonemic) and the category (semantic) fluency tasks.
- The assessment of *executive functions* including cognitive flexibility, selective attention, cognitive inhibition, and information processing speed using the Stroop Test (Stroop, 1935).
- The assessment of *visuo-spatial construction* using the figures from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery (Morris et al., 1988).

All of these tests and scales have been validated and are widely used in the field.

Overall cognitive and functional status was assessed using the Clinical Dementia Rating (CDR) scale, a widely used scale

for the clinical staging of cognitive impairment. The CDR encompasses data about cognitive and functional performance in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris, 1993).

Participants with a global CDR $> = 1$ (defining dementia) were excluded from the current study.

The CDR Sum of Boxes (CDRSOB) was calculated.

Personality Assessment

Personality traits were measured using the Revised NEO Five-Factor Inventory (NEO-FFI-R) in its French version validated in Switzerland (Aluja et al., 2005). The NEO-FFI-R is the short version of the revised NEO Personality Inventory (NEO-PI-R). The questionnaire measures the five main personality dimensions of the Five-Factor Model, i.e., neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Participants were asked to respond to 60 items using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). For each of the five factors, a score is obtained by summing up the scores of the corresponding items (Costa, 1994).

Cortisol Measures

Salivary cortisol has been established as a reliable indicator of circulating cortisol levels and HPA axis function (Gallagher et al., 2006). Participants used Salivette sampling devices (Sarstedt, Rommelsdorf, Germany) for saliva collection.

Four salivary samples were obtained from each participant: upon waking, 30 min after waking, at 11 am and at 8 pm. Subjects were instructed not to brush their teeth and to refrain from eating, drinking, smoking, and exercising 30 min prior to and during the self-administered sampling procedure (Kuehner et al., 2007). Subjects were also instructed to keep a saliva collection sheet where they would record adherence to the protocol including exact time of saliva collections. Until sampling had been completed, subjects stored the saliva samples at home in their freezers before returning them to the laboratory together with the saliva protocol, where they were stored at −20°C until biochemical analysis.

Free cortisol levels in the salivary samples were measured using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variability were <9%.

In case of non-adherence to the protocol, missing values were analyzed using the expectation-maximization algorithm.

We calculated cortisol Area Under the Curve (AUC) using the trapezoid formula (Pruessner et al., 2003). The AUC is a commonly used measure to estimate total hormonal output over a period of time. Unlike other summary measures such as mean cortisol, the AUC captures not only the cortisol levels at the times of sampling but also changes over time (Pruessner et al., 2003).

We also calculated the cortisol awakening response (CAR) defined as the difference between cortisol 30 min after waking and cortisol upon waking.

Other Variables

Subjective cognitive decline was assessed using the Cognitive Complaint Questionnaire (QPC) (Thomas-Antérion et al., 2003). The QPC is a French-language rater-administered instrument consisting of 10 yes/no questions assessing subjective cognitive changes over the previous 6 months. According to the scoring method proposed by the authors, subjective cognitive decline is considered present if the participant gave at least three positive answers to the 10 questions and/or a positive answer to question 5 and/or at least two positive answers to questions A,4,5,7,8.

Depressive symptoms were assessed at physical evaluation (approximately 1 year before the cognitive assessment) using the Center for Epidemiologic Studies Depression scale (CES-D) in its French version (Morin et al., 2011). CES-D scores range between 0 and 60 with higher scores indicating more depressive symptoms. Depressive symptoms were clinically re-assessed at the same time as the cognitive assessment.

Level of formal *education* was categorized into two groups: primary/secondary school education and higher education.

Body Mass Index (BMI) was also included as a covariate since cortisol levels might depend on BMI (Odeniyi et al., 2015).

Ethics Statement

The CoLaus/PsyCoLaus study was approved by the Ethics Committee of the University of Lausanne and written informed consent was obtained from all participants.

Statistical Analysis

Statistical analysis was performed using SPSS v23.0 (IBM Corp., Armonk, NY, USA).

Descriptive Statistics

Continuous variables were described as mean ± standard deviation, while categorical variables were described through absolute and relative frequencies.

The scores of each cognitive domain (memory, fluency, executive functions and visuo-spatial construction) were standardized (z-scores were calculated for the sum of each cognitive domain score).

Associations between Cognitive Performance and Cortisol

Hierarchical multiple linear regression models were constructed with the MMSE score as an outcome variable and with the cortisol AUC then the CAR (respectively) as independent variables, controlling for age, sex, BMI, education and CES-D score.

Afterward, each cognitive domain z-score was considered as a dependant variable with cortisol AUC then CAR (respectively) as independent variables, controlling for age, sex, BMI, education and CES-D score.

Associations between Cognitive Performance and Personality Traits

Hierarchical multiple logistic regression models were constructed with the MMSE score, then with the CDRSOB and each cognitive domain z-score respectively as dependent variables, and with the

NEO-FFI-R trait scores as independent variables, controlling for age, sex, BMI, education and CES-D score.

Associations between Cortisol and Personality Traits

Hierarchical multiple logistic regression models were constructed with the cortisol AUC then with the CAR respectively as dependent variables, and with the NEO-FFI-R trait scores as independent variables, controlling for age, sex, BMI, education and CES-D score.

Associations between Cognitive Performance, Cortisol and Personality Traits

A three-block hierarchical multiple regression model was constructed with the MMSE score as a dependant variable. Block one included age, sex, BMI, education and the CES-D score. Block two included the NEO-FFI-R trait scores and the interaction between NEO-FFI-R trait scores and the cortisol AUC and block three the cortisol AUC.

For each of these regression models, the unstandardized regression coefficients (B), their 95% confidence intervals (CIs), the corresponding R squares (R^2) and the *p*-values are presented.

The mediation hypothesis was assessed using Sobel's method (Sobel, 1982).

For multiple comparisons, *p*-values were adjusted according to Holm–Bonferroni's method.

RESULTS

Characteristics of the Sample

Of the 1918 subjects aged at least 65 at the first follow-up visit of CoLaus/PsyCoLaus, 1214 had a thorough cognitive assessment and 643 non-demented (CDR score < 1) individuals also agreed to provide salivary samples and underwent a personality assessment (33.5% of all participants in this age range) (**Figure 1**).

Compared with the whole PsyCoLaus sample aged at least 65, our sub-sample had a comparable distribution by age, gender, education level, BMI and CES-D score (**Table 1**).

Among the salivary cortisol measures, 164 (6.4% of the total number of values) were missing.

The results of the different cognitive scores, the personality assessment as well as the cortisol measures are described in **Table 2**.

Subjective cognitive decline was not associated with cortisol, cognition, depression or personality traits, and was not included in further statistical analysis.

Table 3 shows the Spearman's correlations between the Big Five traits in our population. Although the correlations were significant, they were modest, and induced no multicollinearity issues in regression models as checked by tolerance.

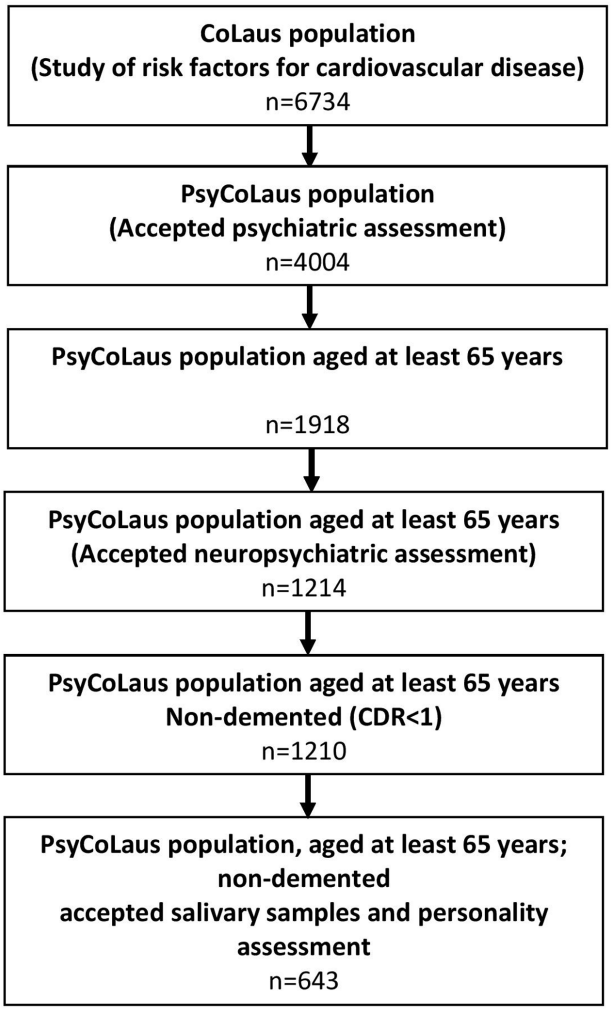

FIGURE 1 | Flow chart of the included participants.

TABLE 1 | General characteristics of the studied samples.

	PsyCoLaus sample aged at least 65	Studied sample	*p*
n	1214	643	
Age, years (m ± SD)	71.6 ± 4.7	71.5 ± 4.5	0.66
Gender, % women	57.9	57.7	0.93
Education level, % higher education	40.5	38.3	0.36
BMI, Kg/m^2 (m ± SD)	26.9 ± 4.7	26.7 ± 4.5	0.38
CES-D score (m ± SD)	10.3 ± 8.2	10.0 ± 7.9	0.45

m, mean; SD, standard deviation; BMI, Body Mass Index; CES-D, Center for Epidemiologic Studies Depression Scale.

Personality Traits and Cortisol

Cortisol AUC was associated negatively with extraversion ($p = 0.005$; slope = −2.850 [−4.854; −0.846]) and positively with openness ($p = 0.008$; slope = 2.412 [0.628; 4.197]; $R^2 = 0.030$) after controlling for age, sex, depressive symptoms and BMI.

Cortisol awakening response was negatively associated with the neuroticism score ($p = 0.048$; slope = −1.117 [−2.222; −0.011]; $R^2 = 0.031$) after controlling for age, sex, depression, education and BMI.

TABLE 2 | Cognitive, personality and cortisol profile of the studied population.

MMSE score (0–30) (m ± *SD*)	29.2 ± 1.6
CDRSOB median (P25;P75)	0.5 (1.0; 1.5)
CDR score, n(%)	
0	291 (45.3)
0.5	352 (54.7)
QPC, subjective cognitive decline present, n(%)	42 (21.0)
DMT (m ± *SD*)	
Immediate recall (0–16)	15.8 ± 1.1
Total free recall (0–48)	29.8 ± 6.9
Total cued recall (0–48)*	18.0 ± 9.2
Identification (0–16)	15.9 ± 0.4
Recognition (0–48)	44.8 ± 9.4
Delayed free recall (0–16)	11.6 ± 2.6
Delayed cued recall (0–16)*	4.9 ± 3.7
DO40 picture-naming test (0–40) (m ± *SD*)	39.7 ± 1.2
Semantic verbal fluency (m ± *SD*)	29.5 ± 8.1
Phonemic verbal fluency (m ± *SD*)	20.9 ± 7.8
Stroop test, correct items (m ± *SD*)	23.9 ± 0.6
Stroop dots condition (0–24)	23.9 ± 0.6
Stroop words condition (0–24)	23.9 ± 0.4
Stroop interference condition (0–24)	23.2 ± 1.9
CERAD figures (0–11) (m ± *SD*)	10.5 ± 1.0
NEO-FFI	
Neuroticism (0–48) (m ± *SD*)	17.3 ± 6.7
Extraversion (0–48) (m ± *SD*)	27.3 ± 6.0
Openness (0–48) (m ± *SD*)	29.0 ± 5.6
Agreeableness (0–48) (m ± *SD*)	33.8 ± 5.1
Consciousness (0–48) (m ± *SD*)	34.6 ± 5.4
Cortisol AUC, in μmol.h/L (m ± *SD*)	0.28 ± 0.11
CAR, in nmol/L, median (P25;P75)	6.3 (−0.5; 12.7)

m, mean; SD, standard deviation; CDR, Clinical Dementia Rating; CDRSOB, Clinical Dementia Rating Sum Of Boxes; QPC, Cognitive Complaint Questionnaire; MMSE, Mini Mental State Examination; DMT, Grober and Buschke Double Memory Test; DO40: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NEO Five-Factor Inventory; AUC, Area Under the Curve; CAR, Cortisol Awakening Response.

**Cued recall scores refer to the number of additional items recalled with cues after the free recall step.*

Personality Traits and Cognitive Performance

No association was found between personality traits and the CDRSOB or the MMSE score, controlling for age, sex, depression, education and BMI.

Among the cognitive domains, only the executive functioning domain *z*-score was negatively associated with agreeableness ($p = 0.005$; slope $= -0.107$ [-0.181; -0.033]) and openness ($p = 0.029$; slope $= -0.081$ [-0.154; -0.008]; $R^2 = 0.107$) after controlling for age, sex, depression, education and BMI.

Cognitive Performance and Cortisol

The CDRSOB was positively associated with the cortisol AUC after controlling for age, sex, BMI, education and depressive symptoms ($p = 0.003$; slope $= 0.686$ [0.240; 1.333]; $R^2 = 0.089$) (**Figure 2**). Similarly, the MMSE score was negatively associated with the cortisol AUC, after controlling for age, sex, BMI, education and depressive symptoms (regression $p = 0.039$; slope $= -1.079$ [-2.106; -0.052]; $R^2 = -0.039$) These associations became not significant, however, when the individuals with a cortisol AUC above the 95th percentile are excluded.

Among the cognitive domains, only the memory domain *z*-score was significantly associated with cortisol AUC ($p = 0.025$; slope $= -0.791$ [-1.485; -0.098]; $R^2 = 0.083$). Neither the MMSE score nor any of the cognitive domain *z*-scores was associated with the CAR.

Are Personality Traits Related to the Cortisol AUC Thereby Affecting Global Cognitive Performance?

The CDRSOB score was positively associated with the cortisol AUC after controlling for age, sex, BMI, education and depression, ($p = 0.003$; slope $= 0.686$ [0.240; 1.333]; $R^2 = 0.089$). This association remained significant after controlling for personality traits and for the interaction between personality traits and the cortisol AUC ($p = 0.006$; slope $= 0.792$ [0.233; 1.352]; $R^2 = 0.107$) (**Figure 2**). Sobel test for mediation was not significant.

Post hoc power analysis found an observed statistical power of 0.993.

DISCUSSION

We analyzed the relationships between personality traits, cortisol levels and cognitive performance in a large sample of non-demented subjects aged 65 years or more from the general population. While higher cortisol was associated both with some traits (low extraversion and high openness) and with poorer cognition, our results suggest that cortisol does not mediate the relationship between personality traits and cognition.

Personality Traits and Cortisol

In our study, individuals with higher openness tended to have higher cortisol levels. This finding is in line with Bibbey et al.'s (2013) study which showed that participants who were less open had smaller cortisol reaction to stress. Yet, other studies did not find any association between openness and cortisol (LeBlanc and Ducharme, 2005; Gerritsen et al., 2009; van Santen et al., 2011). This discrepancy is likely explained by different studied populations.

Lower extraversion was associated with higher cortisol levels. Since extraversion is associated with warmth, assertiveness and positive emotions (LeBlanc and Ducharme, 2005), we might expect extravert individuals to deal better with stress and thus to have higher thresholds to activate their HPA axis. However, previous studies either showed an opposite tendency (higher extraversion associated with higher cortisol) (Miller et al., 1999; LeBlanc and Ducharme, 2005), or found no significant association (Ballenger et al., 1983; Schommer et al., 1999).

We did not find any link between neuroticism and cortisol. While this result is similar to that of some other studies (Adler

TABLE 3 | Spearman correlations between the Big Five traits in the studied population.

		Neuroticism	Extraversion	Openness	Agreeableness	Conscientiousness
Neuroticism	ρ* *p*	–	−0.391 <0.001	−0.165 <0.001	−0.276 <0.001	−0.401 <0.001
Extraversion	ρ* *p*		–	0.271 <0.001	0.244 <0.001	0.426 <0.001
Openness	ρ* *p*			–	0.178 <0.001	0.171 <0.001
Agreeableness	ρ* *p*				–	0.320 <0.001

* ρ, *Spearman's correlation coefficient.*

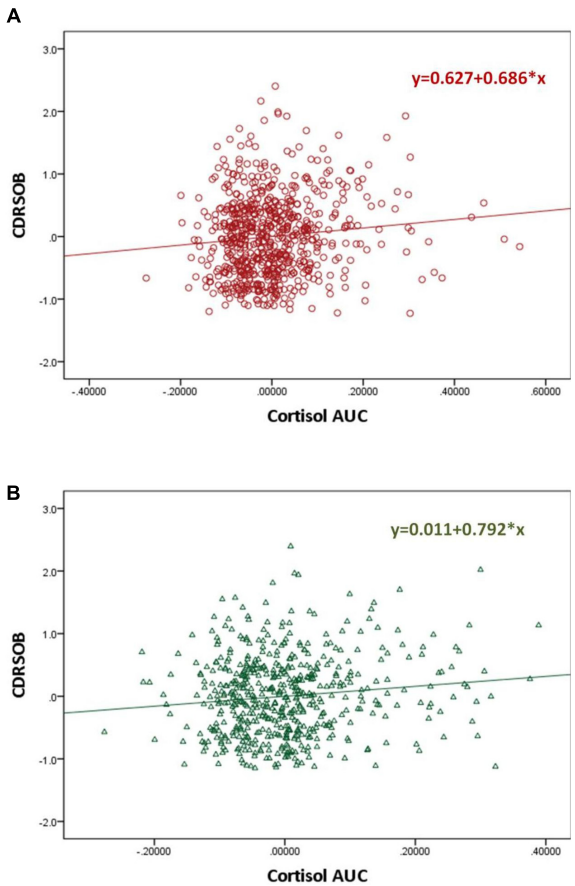

FIGURE 2 | Scatter plot graphs of partial regression analysis result for the association between the MMSE and Cortisol Area Under the Curve before (A) and after **(B)** controlling for personality Big Five traits and the interaction between Big Five traits and the cortisol AUC*

et al., 1997; Schommer et al., 1999; Ferguson, 2008), neuroticism has often been associated with elevated cortisol (Bridges and Jones, 1968; van Eck et al., 1996; Miller et al., 1999; Portella et al., 2005; Yoshino et al., 2005; Gerritsen et al., 2009; Nater et al., 2010; Garcia-Banda et al., 2014; Miller et al., 2016), yet also with decreased cortisol (Ballenger et al., 1983; LeBlanc and Ducharme, 2005).

This discrepancy is probably due to different studied populations and to the effects of depression and anxiety which have been controlled for in some studies but not in others.

Personality Traits and Cognitive Performance

We did not find any relationship between the MMSE score or the CDRSOB and personality traits. In our study, we considered all of the Big Five factors, whereas most prior studies examining the link between cognition and personality traits focused solely on neuroticism and a few additionally examined extraversion.

Higher neuroticism has been reported to be associated with lower MMSE scores in older primary care patients independently of depression (Boyle et al., 2010) as well as community-dwelling individuals aged at least 70 years independently of depression and anxiety (Jorm et al., 1993). This association might be stronger in demented subjects but seems to be also present among non-demented individuals (Jorm et al., 1993). Higher neuroticism seems to be associated with poorer episodic memory in community-dwelling individuals (Jorm et al., 1993; Meier et al., 2002; Klaming et al., 2016) as well as in patients with AD (Wilson et al., 2004). Higher neuroticism has been shown to be linked to an increased risk of incident AD dementia (Terracciano et al., 2014).

Data about the association between extraversion and cognitive measures have been scarce and discrepant. Indeed, Meier et al. found that extraversion positively correlated with episodic memory performance (Meier et al., 2002). This link was explained by more extraverted older adults being probably more stimulated and less affected by the loss of social interactions that occurs with age (Meier et al., 2002). However, others did not find any link between cognition and extraversion (Jorm et al., 1993).

A meta-analysis examining personality traits and the risk for AD showed that higher agreeableness could be a protective factor against AD (Terracciano et al., 2014).

Moreover, since agreeableness is characterized by altruism and kindheartedness, agreeable people might be more inclined to deal positively with stressors. Hence, individuals with low agreeableness are probably more prone to react negatively to stressors, in the same way as people with high neuroticism, thus explaining our finding (Parent-Lamarche and Marchand, 2015).

We found that individuals scoring higher on agreeableness or openness had poorer executive functioning. This result is in line with Ikeda et al.'s (2014) study reporting an association between higher agreeableness scores and weakened suppression of the default mode network. This network consists of the posterior cingulate cortex and precuneus, the inferior parietal cortices, and dorsal and ventral areas of the medial frontal cortex and is normally suppressed during frontal tasks (Ikeda et al., 2014).

Finally, we did not find any association between conscientiousness and cognition, while a clinical and autopsy study, found higher premorbid conscientiousness in demented patients with cerebral AD pathology compared to non-demented individuals with cerebral AD pathology (Terracciano et al., 2014).

Are Personality Traits Related to the Cortisol AUC Thereby Affecting Global Cognitive Performance?

Specific personality traits might alter cognition and/or increase the risk for AD through increased cortisol output. Indeed, as personality traits affect the way individuals cope with stressors they might modulate the effects of the various stressors over the lifespan on the HPA axis. At the same time, elevated cortisol has commonly been associated with cognitive impairment (Lupien et al., 2007; Lee et al., 2008; Tatomir et al., 2014; Geerlings et al., 2015; Vogel et al., 2016), hippocampal atrophy (Sapolsky, 2000; Tatomir et al., 2014) and AD pathology (Green et al., 2006).

Our findings suggest that personality traits might not mediate or modify the association between cortisol and cognitive performance. Certain personality traits might lead to poorer cognitive performance, independently of cortisol, through other mechanisms including higher rates of cigarette smoking, physical inactivity, obesity and depression which in turn are known risk factors for dementia, as well as effects on inflammatory markers (particularly, IL6, CRP and leucocyte count) and neurotrophic factors. Furthermore, shared genetic liability (involving the *DYRK1A* and the APOE genes) has also been suggested as a possible mechanism for the association between specific personality traits and AD pathology (Terracciano et al., 2014).

The association we found between cortisol and cognitive performance can be explained by factors other than stress increasing cortisol output more or less depending on the personality traits. Indeed, increased cortisol is associated with the metabolic syndrome, which is tightly linked to vascular dementia and AD (Kim and Feldman, 2015). Moreover, since the hippocampus normally inhibits the HPA axis, the hippocampal atrophy associated with AD might promote the cortisol release (Geerlings et al., 2015).

Strengths and Limitations

Major strengths of this study include its population-based design, the large sample size for this type of studies (many other studies had fewer than 100 participants) as well as the detailed neuropsychological examination. While many other studies only examined one or two personality traits, mainly neuroticism, we assessed the Big Five personality traits. A previous personality assessment allowed us to disentangle effects of pre-morbid personality traits from personality changes associated with cognitive decline.

Nevertheless, some limitations are to be acknowledged. First, the cross-sectional design does not allow us to draw any conclusions about cause-to-effect relationships. Second, only 33.5% of the participants of 65 years and older underwent both the cognitive and the personality assessments and the cortisol measures. However, the included sub-sample had a comparable distribution by age, gender, education level, BMI and CES-D score with the whole PsyCoLaus sample aged at least 65. Third, since the assessment of personality traits was cross-sectional, it does not allow us to draw any conclusions on whether the measured traits were the "stable" adult traits or the traits already modified by a potential neurodegenerative process. Indeed, personality changes seem to occur early in the course of neurocognitive disorders, at the stage of MCI (Donati et al., 2013), although these changes seem to remain moderate. Fourth, we did not collect information about perceived stress at the moment of the study. Different levels of perceived stress might have affected the cortisol levels.

CONCLUSION

High agreeableness and openness might be associated with poorer executive performance. High extraversion and low openness might be associated with increased cortisol. The association between personality traits and cognitive impairment seems to be independent of increased cortisol production and its effects on cognition. Hence, specific personality traits may influence cognition through other mechanisms. According to other studies, these mechanisms may include effects on lifestyle and health related behavior including smoking, dietary habits and physical activity with consequences for cardiovascular risk and the production of cytokines and neurotrophic factors.

AUTHOR CONTRIBUTIONS

Conception and design of the study: SO, EC, AvG, PV, MP, and JP. Data analysis/interpretation: SO, EC, MP, and JP. Drafting the article: SO and JP. Revising the article: SO, EC, AvG, PV, MP, and JP.

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MRI-Based Classification Models in Prediction of Mild Cognitive Impairment and Dementia in Late-Life Depression

Aleksandra K. Lebedeva[1], Eric Westman[1], Tom Borza[2,3], Mona K. Beyer[4], Knut Engedal[5,6], Dag Aarsland[1,7,8], Geir Selbaek[2,3,5,6] and Asta K. Haberg[9,10] for the Alzheimer's Disease Neuroimaging Initiative[†]*

[1] Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden, [2] Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, Brumunddal, Norway, [3] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway, [4] Department of Radiology and Nuclear Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [5] Department of Geriatric Medicine, Oslo University Hospital, Tønsberg, Norway, [6] Oslo and Norwegian National Advisory Unit for Aging and Health, Tønsberg, Norway, [7] Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK, [8] Center for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway, [9] Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway, [10] Department of Radiology and Nuclear Medicine, St. Olav's University Hospital, Trondheim, Norway

Objective: Late-life depression (LLD) is associated with development of different types of dementia. Identification of LLD patients, who will develop cognitive decline, i.e., the early stage of dementia would help to implement interventions earlier. The purpose of this study was to assess whether structural brain magnetic resonance imaging (MRI) in LLD patients can predict mild cognitive impairment (MCI) or dementia 1 year prior to the diagnosis.

Methods: LLD patients underwent brain MRI at baseline and repeated clinical assessment after 1-year. Structural brain measurements were obtained using Freesurfer software (v. 5.1) from the T1W brain MRI images. MRI-based Random Forest classifier was used to discriminate between LLD who developed MCI or dementia after 1-year follow-up and cognitively stable LLD. Additionally, a previously established Random Forest model trained on 185 patients with Alzheimer's disease (AD) vs. 225 cognitively normal elderly from the Alzheimer's disease Neuroimaging Initiative was tested on the LLD data set (ADNI model).

Results: MCI and dementia diagnoses were predicted in LLD patients with 76%/68%/84% accuracy/sensitivity/specificity. Adding the baseline Mini-Mental State Examination (MMSE) scores to the models improved accuracy/sensitivity/specificity to 81%/75%/86%. The best model predicted MCI status alone using MRI and baseline MMSE scores with accuracy/sensitivity/specificity of 89%/85%/90%. The most important region for all the models was right ventral diencephalon, including

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****Correspondence:***
Aleksandra K. Lebedeva
aleksandra.ki.lebedeva@gmail.com

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Abbreviations: CC, corpus callosum; CTH, cortical thickness; LLD, late-life depression; RF, random forest method; R-HC, right hippocampus; R-VD, right ventral diencephalon; SV, subcortical volumetric measurement.

[†]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

hypothalamus. Its volume correlated negatively with the number of depressive episodes. ADNI model trained on AD vs. Controls using SV could predict MCI-DEM patients with 67% accuracy.

Conclusion: LDD patients developing MCI and dementia can be discriminated from LLD patients remaining cognitively stable with good accuracy based on baseline structural MRI alone. Baseline MMSE score improves prediction accuracy. Ventral diencephalon, including the hypothalamus might play an important role in preservation of cognitive functions in LLD.

Keywords: depression, MCI, Alzheimer's disease, Freesurfer, neurodegeneration, hypothalamus, ventral diencephalon, depressive episodes

INTRODUCTION

Depression is associated with accelerated brain aging (Simon et al., 2006; McKinney and Sibille, 2013; Koutsouleris et al., 2014), and is a risk factor for different types of dementia (Aziz and Steffens, 2013; Diniz et al., 2013; Byers and Yaffe, 2014; Cooper et al., 2015; Mourao et al., 2015).

Unfortunately, early identification of predementia states in people with LLD is challenging as reduced cognitive scores can be confounded by the depressive state. Thus depression is an exclusion criterion for some definitions of mild cognitive impairment (MCI; Steffens et al., 2006). It is challenging to predict whether cognitive impairment identified during a depressive episode in a LLD patient will improve after treatment of depression or will progress to dementia. However, it is known that among seniors with MCI identified during a depressive episode only 17% experienced cognitive improvement after 2 years of follow-up (Steffens et al., 2009). Early identification of those LLD patients with increased risk of progressive cognitive decline could allow for more targeted clinical actions, for instance choice of antidepressant (du Jardin et al., 2016; García-Fuster and García-Sevilla, 2016) or other interventions, (Ngandu et al., 2015) and possibly neuroprotective drugs in the future.

Biomarkers known from Alzheimer's disease (AD) research may be used to identify a neurodegenerative process and/or increased risk of developing dementia in LLD patients in particular during a depressive episode when neurocognitive functions may not be reliably assessed. The biomarkers include amyloid-beta positron emission tomography (PET) brain imaging, magnetic resonance imaging (MRI) based cortical and subcortical structural measurements, cerebrospinal fluid tau, and amyloid-beta levels (American Psychiatric Association, 2013; Dickerson and Wolk, 2013). However, it is still not known if these biomarkers can be utilized to identify or predict future cognitive impairment (MCI or dementia status) in LLD.

The aims of this study were: (1) To assess whether structural T1 weighted (T1W) 3D brain MRI obtained during the depressive episode in LLD patients can discriminate LLD who were diagnosed with MCI or dementia after 1-year follow-up from cognitively stable LLD using Random Forest classifier. (2) To identify which regions are affected in LLD with subsequent cognitive impairment. (3) To evaluate the feasibility of using biomarkers derived from AD research, by implementing a classifier trained on structural 3D brain MRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) sample.

MATERIALS AND METHODS

Cohorts

Two cohorts were used in this study:

(1) PRODE (Prognosis of depression in the elderly) – was used as the main cohort (Borza et al., 2015). The PRODE study is a prospective multicenter study including 169 patients ≥60 years referred to treatment for depression at nine centers of geriatric psychiatry in Norway (Borza et al., 2015). Exclusion criteria were life threatening diseases and severe aphasia (as it would reduce the validity of the neuropsychological assessment). Clinical and neuropsychological data were collected using standardized clinical, psychiatric, and neuropsychological assessment (see below). Of the 169 patients, 126 underwent brain MRI examination at inclusion (Lebedeva et al., 2015) T1W 3D brain MRI images were available for 112 patients (**Figure 1**).

(2) ADNI – An established classification model based on RF trained to discriminate between patients with AD ($n = 185$) and healthy controls (HC, $n = 225$) using Freesurfer (v. 5.1) measurements from T1W 3D brain MRI was also used on the PRODE dataset. The training data was obtained from the ADNI database[1]. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. AD patients met the NINCDS/ADRDA criteria for probable AD. The T1W 3D MRI-Freesurfer based model had AD vs. HC accuracy of 90% for the testing dataset and predicted conversion in additional sample of MCI ($n = 165$) to AD with accuracy 79%. The most important regions for the discrimination were: left and right hippocampi, left amygdala, left and right entorhinal cortices, and left inferior temporal cortex (Lebedev et al., 2014). We hypothesized that this model could be used to predict MCI/AD conversion in the PRODE cohort.

[1] adni.loni.usc.edu

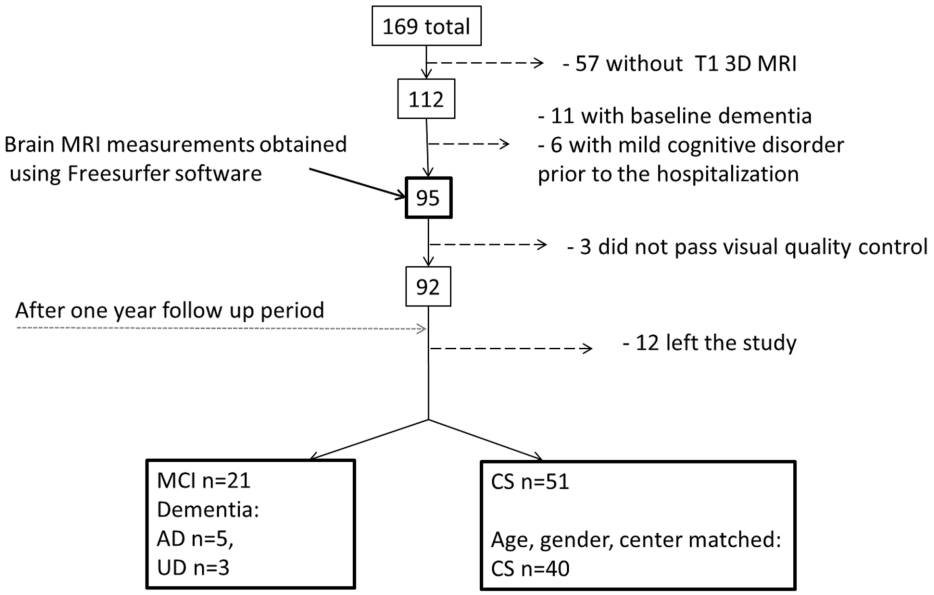

FIGURE 1 | Flow chart describing patient selection and attrition from admission to 1-year follow-up assessment. AD, Alzheimer's disease; UD, Unspecified dementia; MCI, mild cognitive impairment; CS, cognitively stable control group; mild cognitive disorder – F 06.7 (ICD-10).

Clinical and Neuropsychological Assessment

Psychiatric evaluation and neuropsychological assessment were performed three times: at admission to the department of geriatric psychiatry (baseline) and discharge, and after 1-year. At each participating center trained clinicians performed the psychiatric and neuropsychological assessments using a harmonized procedure and the same protocol (Borza et al., 2015).

Clinical assessments included: demographic information, history of depression or other psychiatric condition, family history of psychiatric problems, current psychiatric problems, and treatment(s). Patients were diagnosed based on the criteria of the 10th Revision of the International Classification of Diseases and Health Related Problems (ICD-10; World Health Organization [WHO], 1993). Cognition was measured with the Mini Mental Status Examination, MMSE (Folstein et al., 1975) and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-16; Jorm and Jacomb, 1989). At the 1-year follow-up assessment patients were also diagnosed using Winblad's criteria for MCI (Winblad et al., 2004).

Patient Selection

Patients without dementia diagnoses according to ICD-10 criteria at inclusion and a T1W 3D/structural brain MRI were included in this study (n = 95, **Figure 1**). Not all the patients could be included in the final analyses for a variety of reasons, as specified in **Figure 1**. Based on the 1-year follow-up diagnosis the patients were divided into one mild cognitive impairment-dementia (MCI-DEM) group including those diagnosed with either MCI (n = 21; Winblad et al., 2004) or dementia (n = 8, including: Alzheimer's disease n = 5, unspecified dementia n = 3) [World Health Organization (WHO)]. A matched cognitively stable (CS) group was selected from the remaining 51 patient based on age and gender (n = 40) and controlling for the balance in number of CS and MCI at each center of inclusion (**Figure 1**).

Ethics Statement

The participating patients and caregivers were given oral and written information, and they subsequently gave their written consent to participate. The PRODE study was approved by Regional Committee of Medical Research Ethics and Privacy and Data Protection Officer at Oslo University Hospital (approval number 2009/1774).

MRI

MRI Acquisition

All scans were optimized and harmonized across centers based on American College of Radiology (ACR) phantom and a healthy volunteer. This study is based on T1 3D brain MRI obtained with sagittal volumetric magnetization-prepared rapid gradient echo (3D MP-RAGE) images using the ADNI T1W volume protocol (Jack et al., 2008) in six PRODE centers with 1.5T and 3T MRI scanners (see Supplementary Table S1). Inter-site reliability for the six centers was estimated using the intra-class correlation coefficient (ICC) using two-way random effect model with absolute agreement (McGraw and Wong, 1996). ICC was estimated for the average CTH and total volume of subcortical structures (TSV) obtained from the Freesurfer parcellation and segmentation (see below). Reliability test was performed using SPSS software v. 22. Assessment showed acceptable results (Fleiss, 1986). ICC (CTH) = 0.88 and ICC (TSV) = 0.98. It has been shown that Freesurfer output measurements are consistent between 1.5T and 3T MRI (Han et al., 2006; Pfefferbaum et al.,

2012), thus the data across the field strengths was merged. CS group was matched on number of participants having 1.5 and 3T scans in addition to the other criteria.

Image Processing

Cortical thickness and SV were used as main outcomes. The T1W 3D MRI brain images were processed using Freesurfer (v. 5.1), where regional cortical thicknesses and volumetric measures were estimated. The software is well documented and available for download online[2]. The processing steps included cortical reconstruction and segmentation of gray matter volumetric structures. This was followed by parcellation of the cerebral cortex into units based on gyral and sulcal structure (Destrieux et al., 2010). One hundred forty eight CTH measures (74 from each hemisphere) and 54 regional volumes were generated. All output was visually inspected for segmentation and parcellation quality before the analysis. Volumes of left and right white matter hypointensities, optic chiasm, right and left vessel, and left and right choroid plexus were excluded from further analysis. List of measurements included in the analysis is provided in Supplementary Table S2. The accuracy of the CTH and hippocampal volumes measurements derived by this technique has been validated by histological and manual measurements (Rosas et al., 2002; Sánchez-Benavides et al., 2010). All volumetric structures were normalized by the subject's intracranial volume using the residual approach (Jack et al., 1989). Brain structures in the left and right hemisphere may have different degree of atrophy, thus CTH and SV of the left and right hemisphere were treated separately (Dolcos et al., 2002). Workflow is represented in **Figure 2**.

Statistical Analysis

R programming language (R Core Team, 2016), version 3.3.0, was used to compare demographic and clinical data, and to create random-forest algorithm (RF) classification models. For group comparisons of demographic and clinical variables, the chi-squared test was used for categorical variables, and *t*-test or Mann–Whitney where appropriate for continuous variables. RF classification models were established using R packages "random forest" (Liaw and Wiener, 2002) and "caret" (Kuhn et al., 2016), ROC-curve and area under the ROC-curve (AUC) were estimated and plotted using "pROC" package (Robin et al., 2011). Regions important for the classification were correlated with clinical and demographic variables.

Random Forest Algorithm and Performance Assessment

Random forest method allows performing supervised classifications based on an ensemble of classification trees (Breiman, 2001). RF selects a bootstrapped subset of all observations – about 66% per tree and random subset of all predictors/features (here: CTH, SV) at each node of the tree. RF uses the majority vote of its trees terminal nodes to predict the class label of a new observation. Each tree casts a unit vote for the class. Thus, high numbers of decision trees are expected to increase reliability of the results. For each predictor a Gini index is estimated at each node. Overall importance of a predictor for the model is based on the summation of the decreases in the Gini index at each node (Breiman, 2001). The remaining 33% of the data, i.e., out-of-bag (OOB) data, is used to measure the RF performance. The classification error of the OOB observations is referred to as OOB error (Breiman, 1996). Kappa is another measure of performance demonstrating how close the RF classifications were to the actual classes, controlling for the accuracy of a random classifier as measured by the expected accuracy. Kappa is suggested to provide more reliable information regarding the classifier performance than actual accuracy in case of different class distribution in the dataset (Fleiss, 1971).

RF Procedure

Random forest method algorithm was used to discriminate between the MCI-DEM or MCI and CS groups at 1-year follow-up based on the CTH and SV measures separately and combined. In addition, demographic and clinical information was added to the models to test if performance could be further improved. Only the clinical information obtained at inclusion was used to assess if MCI-DEM statuses 1-year later could be predicted based on the earliest available clinical data and in the depressive state.

PRODE Cohort Models

PRODE models

Five thousand decision trees were used in the RF classification models. RF models were trained to discriminate between MCI-DEM ($n = 29$) or MCI alone ($n = 21$) and corresponding CS patients. When discriminating between MCI vs. CS, the number of CS was reduced to 30 (from 40) matched on age and gender and scanner field strength, in order to keep balance in group class distribution. AUC, sensitivity/specificity, overall accuracy, and kappa, were used to assess performance of the models. Confidence intervals (CI) were estimated using bootstrapping ($n = 100$). The most relevant structures for prediction of MCI-DEM or MCI were correlated with clinical variables related to depression in order to detect regions involved in both pathological processes.

ADNI cohort models

The previously established ADNI model (Lebedev et al., 2014) was implemented in the PRODE dataset to evaluate its ability to discriminate between MCI-DEM ($n = 29$) and CS group ($n = 51$). However, we did not expect the ADNI model to outperform the PRODE models because it was trained on a data derived from AD patients versus HC, not LLD and not converting to MCI.

RESULTS

Demographics

Clinical and demographic variables in MCI-DEM and CS groups are provided in **Table 1**. MCI-DEM group had significantly lower MMSE scores at all three time points compared with

[2]http://surfer.nmr.mgh.harvard.edu/

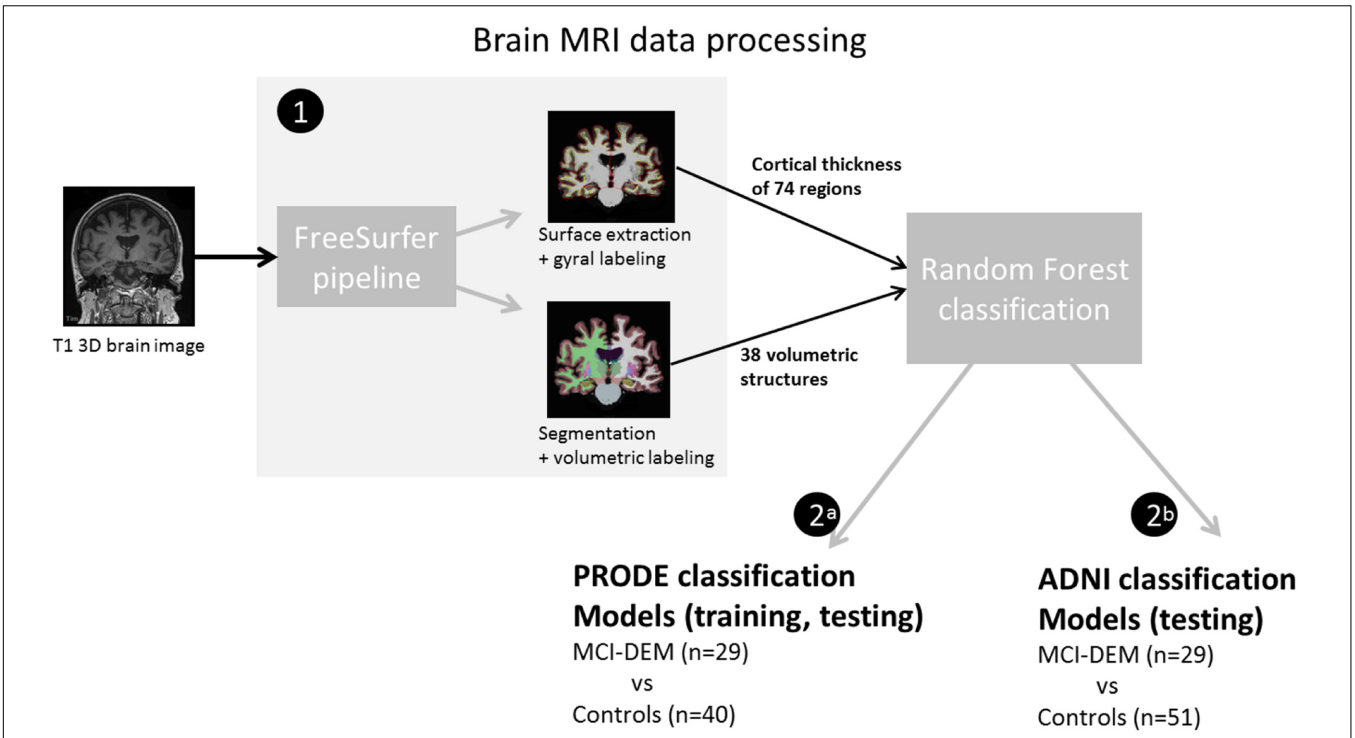

FIGURE 2 | Diagram of the brain magnetic resonance imaging (MRI) data processing (1) T1W 3D MRI brain images were analyzed in Freesurfer software. Resulting measurements where used as input for the random forest classifications. (2a) In the prognosis of depression in the elderly (PRODE) models, PRODE cohort was used as training and testing datasets. **(2b)** The Alzheimer's Disease Neuroimaging Initiative (ADNI) models were trained on the ADNI data (Alzheimer's patients vs. healthy elderly). PRODE cohort was used as testing dataset.

CS group. Other variables did not differ between the groups. Similarly, the MCI group alone did not differ from the matched CS patients in terms of age ($p = 0.21$) or gender ($p = 0.92$). Notably, the standard deviation of the MMSE scores increased in the MCI/dementia group between assessments "at discharge" and "follow-up," reflecting increased variance in their cognitive statuses.

Prediction of MCI and Dementia in LLD

PRODE (MCI-DEM vs. CS Group) Models

The model using SV+CTH as input had the best performance in discrimination between MCI-DEM and CS groups. The model using only SV as input had the best performance in discrimination between MCI (excluding eight dementia patients) and CS groups. Details are provided in **Table 2**. The model using only CTH as input for the MCI vs. CS discrimination had 67% accuracy and sensitivity < 50%. MMSE score at inclusion improved the models performance. Adding age, gender, or education to the model did not affect the results. When excluding patients with MADRS < 7 and MMSE < 26 at discharge ($n = 4$), accuracy changed slightly from 76 to 74% using SV as input.

Brain Measurements Used in Prediction

The most relevant measurements for the models were right ventral diencephalon (R-VD, mean decrease in Gini index = 8.26), middle anterior corpus callosum (mid-anterior CC, mean decrease in Gini index = 2.06) and right hippocampus (R-HC mean decrease in Gini index = 1.47). For all the PRODE models (**Table 2**), the same structures (R-VD, mid-anterior CC, and R-HC) were the most important. When excluding participants from each center, the same structures remained the most important.

Relationship between Ventral Diencephalon and Clinical and Demographic Measures

Right ventral diencephalon, mid-anterior CC, and R-HC volumes were correlated with the number of depressive episodes (adjusting for age, gender, and MMSE). The number of depressive episodes had significant inverse association with R-VD ($p = 0.02$) and mid-anterior CC ($p = 0.04$) volumes. Next, total ventricular volume was added as a covariate to assess if structural changes co-occur with ventricle expansion as an indirect measure of a degenerative nature of the observed structural changes. Adjusting for total ventricular volume negated the effect of number of depressive episodes on R-VD volume ($p = 0.12$) and mid-anterior CC volume ($p = 0.08$). No association was found between the number of depressive episodes and R-HC volume. MMSE score was associated with R-HC volume ($p = 0.03$), but not with R-VD volume ($p = 0.16$) or mid-anterior CC volume ($p = 0.18$).

ADNI (MCI-DEM vs. CS Group) Model

The ADNI model trained on SV demonstrated better performance on separating MCI-DEM vs. CS in the PRODE

TABLE 1 | Demographic and clinical characteristics of the MCI-DEM and cognitively stable (CS) groups.

PRODE data set	MCI-DEM	CS	Test statistics	*p*-value*
N	29	40	–	–
Age – mean (SD)	78.1 (7,3)	76,4 (5,8)	$t = -1.5$	0.31
Sex – n women (%)	22 (75%)	29 (72%)	$\chi^2 = 0.03$	0.85
Education (total years) – mean (*SD*)	8.9 (2.79)	10.1 (2.61)	$t = -1.8$	0,07
Number of depressive episodes – (range)	2.5 (0–4)	1.5 (0–4)	$z = -1.06$	0.28
Age at depression onset – median (range)	29.7 (15–85)	35.0 (16–88)	$z = -1.02$	0.3
MADRS-1 – median (range)	26 (15–52)	27 (0–48)	$z = -0.66$	0.5
MADRS-2	9 (0–31)	7 (0–30)	$z = -0.44$	0.65
MADRS-3	8 (0–35)	4.5 (0–30)	$z = -0.43$	0.66
MMSE-1 – mean (*SD*)	24.6 (3.0)	26.4 (1,8)	$t = -2.71$	0.005
MMSE-2	25 (2.8)	27 (1.9)	$t = -5.42$	0.009
MMSE-3	23.8 (5.6)	28 (1.7)	$t = -5.90$	<0.001

MCI-DEM – LLD patients who received diagnosis of mild cognitive impairment or dementia at 1-year follow-up assessment. CS – LLD patients who remain cognitively stable at 1-year follow-up assessment.
**t-test, Mann–Whitney U test or chi-square test as appropriate.*
MADRS, Montgomery–Asberg Depression Rating Scale; MMSE, Mini Mental State Examination.
MADRS/MMSE – 1 - at inclusion, 2- at discharge, 3- after 1 year follow-up period.

dataset (accuracy = 67.0%) than the ADNI model trained on CTH+SV (accuracy = 57.5%; **Table 2**).

DISCUSSION

In this study, we have demonstrated that LLD patients who were diagnosed with MCI or dementia 1 year later can be discriminated from cognitively stable LLD patients using structural brain measurements with 76% accuracy. The best model predicted MCI status alone using SV and MMSE scores with accuracy/sensitivity/specificity of 89%/85%/90%.

To our knowledge this study is the first to build classification models based on structural MRI measures to predict development of MCI or dementia in LLD patients, and to assess performance of a model trained for AD-HC discrimination (ADNI model) on a LLD dataset (PRODE cohort). We used all brain parenchyma volumes derived from the Freesurfer analysis, and showed that volumes of R-VD, mid-anterior CC, and R-HC were the most important for discrimination between MCI-DEM and CS group.

We have found only one study using a classification approach and MRI data to predict MCI diagnosis, but in non-depressed elderly and based on arterial spin labeling. This study reported that perfusion in a region of interest in the posterior cingular cortex could distinguish those developing MCI from a CS group with an AUC of 66% (Xekardaki et al., 2015).

Brain Regions Important for Prediction of MCI and Dementia Diagnosis

The most important regions for predicting a diagnosis of MCI or dementia after 1-year follow-up were volumes of R-VD, mid-anterior CC, and R-HC, respectively.

Right ventral diencephalon was demonstrated to be the most relevant structure. The ventral diencephalon in Freesurfer includes several structures: hypothalamus with mammillary body, subthalamic, lateral geniculate, medial geniculate and red nuclei, substantia nigra and surrounding white matter. Some of these structures, i.e., substantia nigra and red nuclei, are not locate to the diencephalon but mesencephalon according to standard anatomical nomenclature. The hypothalamus is known to be strongly involved in depression. As a part of hypothalamic–pituitary–adrenal (HPA) axis, it is crucial for emotional behavior and stress response. There are numerous studies showing dysregulation of the HPA axis in depression, but also in aging and neurodegeneration (Sapolsky et al., 1986; Sapolsky, 2000; Varghese and Brown, 2001; Du and Pang, 2015). It has also been proposed that HPA-axis dysfunction is central to the development of AD (Ishii and Iadecola, 2015). Indeed, hypothalamic dysfunction can explain the overlap in symptoms between depression and AD (mood, appetite, sleep, memory, autonomic). Consistent with our finding, several previous imaging studies have shown structural and functional abnormalities in the hypothalamus in MCI, preclinical AD, and AD compared with control groups (Callen et al., 2001; Nestor et al., 2003; Cross et al., 2013; Brueggen et al., 2015). For instance, Hall et al. (2008) have demonstrated reduced basal forebrain and hypothalamus volumes in preclinical AD, and interestingly the combination of reduced forebrain and hippocampal volumes was associated with more rapid cognitive decline. However, to the best of our knowledge the current study is the first study to assess the role of the entire ventral diencephalon in the context of neurodegeneration. There are two previous studies examining the ventral diencephalon (segmented in Freesurfer) in relation to mood disorders. The first showed that bilateral ventral diencephalon volume obtained from Freesurfer was one of three top-ranked endophenotypes of major depressive disorder in an analysis of a high-dimensional set of over 11,000 traits (Glahn et al., 2012). The other study demonstrated that volume of the ventral diencephalon discriminated patients with major depressive disorder from those with bipolar depression as well as controls (Sacchet et al., 2015). Taken together, these

TABLE 2 | Performance of the random forest classification models based on baseline structural magnetic resonance imaging (MRI) measurements with and without Mini-Mental State Examination scores.

Model	AUC (95% CI)	Sens/spec(accuracy)	kappa
PRODE	**Training set: MCI-DEM ($n = 29$) vs. CS group ($n = 40$)***		
SV	0.802 (70.4%–90.0%)	68/84 (74.6)	0.46
CTH+SV	0.758 (64.5%–87.0%)	55/86 (76.0)	0.47
CTH+SV+MMSE1	0.867 (77.5%–95.9%)	75/86 (81.3)	0.61
SV+MMSE1	0.892 (75.1%–96.9%)	75/81 (81.3)	0.60
PRODE	**Training set: MCI ($n = 21$) vs. CS group ($n = 30$)***		
SV	0.773 (64.3%–90.3%)	65/86 (76.4)	0.50
CTH+SV	0.678 (51.78%–83.8%)	52/80 (70.5)	0.44
CTH+SV+MMSE1	0.867 (75.1%–98.2%)	76/90 (86.2)	0.71
SV+MMSE1	0.905 (81.4%–99.6%)	85/90 (90.1)	0.79
ADNI	**Training set: ADNI AD vs. ADNI Controls**		
	Testing set: PRODE MCI-DEM ($n = 29$) vs. PRODE CS group ($n = 51$)**		
SV	0.737 (62.6%–84.7%)	65.5/68.6 (67)	0.40
CTH+SV	0.623 (50.1%–74.4%)	48/62 (57.5)	0.10

PRODE model – trained to discriminate between LLD who developed MCI or dementia and cognitively stable LLD.
ADNI model – trained to discriminate between non-depressed patients with Alzheimer's disease and cognitively normal non-depressed elderly.
CTH, cortical thickness; SV, subcortical volumes; MC, mean curvature; OOB, out-of-bag; AUC, area under the ROC-curve; MMSE1, Mini–Mental State Examination scores at admission; Sens/Spec, Sensitivity/specificity; NA, not applicable.
** Accuracy estimated for OOB set.*
***Accuracy Estimated for the testing dataset.*

findings suggest that neurodegeneration in ventral diencephalon including the hypothalamus might be a link between depression and cognitive impairment.

After R-VD, CC (mid-anterior CC) and hippocampal (R-HC) volumes were the most relevant structures for predicting MCI-DEM. HPA-axis dysregulation is associated with elevated cortisol levels (O'Brien, 1996; Du and Pang, 2015) which is hypothesized to cause reduced CC and hippocampal volumes due to neurotoxic effects (Bao et al., 2008; Liu et al., 2016). The importance of CC volume for predicting MCI-DEM suggests presence of inter-hemispheric disconnection already in the early stages of the neurodegenerative process. Previously, it has been shown that anterior, middle and posterior portions of the CC have less volume in AD compared to controls, but only the middle part was smaller in amnestic MCI compared with controls (Qiu et al., 2016). Moreover, decreased volume of mid-anterior portion of CC has been linked to the memory loss in MCI and AD (Qiu et al., 2016). The present findings support a connection between R-VD, R-HC, and CC pathology in the development of MCI and dementia in LLD, which may be linked to HPA-axis dysregulation. A previous study examining only CC volume reported that structural changes in CC predicted MCI-to-AD conversion after 2.5 years on average (Lee et al., 2016), similar to the current study where a whole brain approach was used and conversion was to MCI/dementia. Hippocampal abnormalities are one of the most replicable findings in both depression and AD (Kempton et al., 2011; Sabuncu et al., 2011). Hippocampus has large bidirectional connection with the mammillary bodies of the hypothalamus which also might explain the concordant changes in these two structures. The limbic-diencephalic pathways, including the mammillothalamic tract and the mammillary bodies *per se* are crucial for episodic memory (Vann and Nelson, 2015; Aggleton et al., 2016). Hypometabolism in the mammillary bodies has been shown in both MCI and AD (Nestor et al., 2003). Limbic-diencephalic pathway dysregulation has been shown in the earliest stages of AD (Acosta-Cabronero and Nestor, 2014). Indeed, limbic regions, which are crucial for emotion processing, are also crucial for episodic memory. Thus, abnormal limbic-diencephalic interaction may be a core feature of in MCI-DEM development in LDD.

Of note, only brain structures from the right hemisphere were important for the classifications. This supports the right hemi-aging model, proposing that the right hemisphere shows greater age-related decline than the left hemisphere (Dolcos et al., 2002). However, this model is based on behavioral data rather than neuroimaging and the evidence has been controversial (Daselaar and Cabeza, 2005).

Interestingly, the number of depressive episodes had significant inverse association with the R-VD and mid-anterior CC volumes. Previously, it was reported that the number of depressive episodes is associated with reduced volume of the dentate gyrus in patients with major depressive disorder (Treadway et al., 2015). It is not known whether reductions of R-VD and mid-anterior CC are developmental phenomena, which leads to increase of the number of depressive episodes or degenerative consequences of a larger number of depressive episodes. However, including total ventricular volume to the regression model negated the effect of the number of depressive episodes on the R-VD volume and reduced on mid-anterior CC, providing indirect evidence for the degenerative nature of R-VD and mid-anterior CC reduction. Future studies using longitudinal imaging data could uncover the causality.

SV+CTH+MMSE Models

MCI-DEM had significantly lower MMSE scores at all three time points compared to the CS group. Regardless of whether cognitive assessment in depressed patients is confounded by depression *per se*, including MMSE scores at admission improved the model's prediction of MCI and dementia. Along with a recent study of Heser et al. (2016), the present results suggest that even during the depressive episode cognitive impairment require clinical attention as a possible sign of incipient dementia. Given the highly significant difference in MMSE scores at all three time points between the MCI/DEM and CS group, the probability that there was a true difference in MMSE scores between MCI-DEM and CS groups at all time points is very high, suggesting that MMSE in an appropriate additional predictor of MCI/AD even in LLD groups.

There was no correlation between MMSE scores R-VD and mid-anterior CC volumes suggesting that MMSE scores did not bias classification results. The absence of correlation between MMSE and the two main predictors suggested that MMSE improved classification models performance by explaining additional factor variance.

Predicting MCI-DEM vs. MCI

The SV model trained on MCI vs. CS demonstrated better performance than the model trained on the mixed sample of MCI-DEM dementia vs. CS. The reasons might be a more heterogeneous pattern of structural brain changes across dementias in the MCI/DEM combined group and presence of larger variability in the stages of pathological process. On the other hand, the CTH+SV model performed better on the mixed MCI+DEM group compared with MCI only. One explanation might be that CTH get altered in the later stages and/or more severe cases of cognitive impairment in LLD and that relevance of the structural brain measurement as a biomarker therefore depends on the stage of the disease.

Predicting MCI-DEM Conversion in LLD Using the ADNI Model

MCI-DEM status was discriminated from the CS group with 67% accuracy using the ADNI model. In other words, patients in the MCI-DEM group were more likely to be classified as cases than those in CS group based on their baseline brain MRI.

Interestingly, the ADNI model trained only on SV had much higher accuracy compared with the one trained on CTH+SV. Taking into account that the most relevant structures for MCI-CS discrimination (PRODE models) were subcortical structures and that the model combining SV with CTH had higher accuracy in MCI-DEM than in MCI alone, the present results may suggest that in LLD patients, who will develop MCI or dementia, neurodegeneration appears to start in subcortical structures and spread up to the neocortex in later stages. In agreement with our findings it has been shown that atrophy in basal forebrain and hypothalamus but not neocortex, precedes clinical symptoms of AD by 4.5–5 years (Brueggen et al., 2015). Several earlier studies have shown hypometabolism restricted to hippocampus and parahippocampal gyrus in MCI, whereas AD had additional temporal neocortical hypometabolism (De Santi et al., 2001; Nestor et al., 2003). Taken together, the current results suggest that classification models for prediction of MCI/preclinical AD should focus on subcortical structures rather than the neocortex.

Limitations

One of the limitations of the present study is that the time interval between MRI assessment and MCI diagnosis was relatively short, thus it is possible that some CS patients could be diagnosed with MCI/dementia at a later time point. Excluding LLD participants with the lowest MADRS and MMSE scores at discharge ($n = 4$) did not alter the results notably (no substantial drop in accuracy) which indicate that the possibility that some patients could receive MCI diagnosis earlier did not bias the results strongly. Another issue is that MMSE might not be sensitive enough to detect MCI. In any case, there are no cognitive screening instruments validated for use in a depressed elderly population according to our knowledge. All the models including only brain measurements as predictors had very good specificity and sufficient sensitivity. One of the reasons for this might be the relatively small sample size. In future studies classification models should be trained on larger samples after longer follow-up periods. Inclusion of MRI scans obtained from scanners with different magnetic field strengths might be considered a limitation; however, it was shown that Freesurfer output measurements are consistent between 1.5T and 3T MRI, which was confirmed in our reliability analysis. We have shown that ICC is high across the centers. We also balanced the number of participants from each center and verified the results excluding each center, in order to assess reliability of the results which were consistent.

Possible Practical Implementation

Our results suggest that LLD with smaller volumes of the R-VD, mid-anterior CC, and R-HC and lower MMSE scores at inclusion have a higher probability of receiving a diagnosis of MCI or dementia the following year. These measurements can provide clinicians with novel evidence for an expected trajectory of cognitive functioning in LLD and help to define a target group for interventions against cognitive decline (Bredesen, 2014).

Future mechanistic studies should verify processes underlying diencephalic neurodegeneration in LLD patients.

AUTHOR CONTRIBUTIONS

AL: Study design, data analyses, interpretation of the results, manuscript writing. EW and DA: Study design, interpretation of the results. TB and KE: Study design, data collection, interpretation of the results. MB: Data collection, interpretation of the results. GS and AH: Data collection, study design, interpretation of the results. All authors participated in manuscript revision and final approval.

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PRODE

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2017.00013/full#supplementary-material

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Reciprocal Associations between Depressive Symptoms and Mastery among Older Adults; Black-White Differences

Shervin Assari[1,2]* *and Maryam M. Lankarani*[3]

[1] Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA, [2] Center for Research on Ethnicity, Culture and Health, School of Public Health, University of Michigan, Ann Arbor, MI, USA, [3] Medicine and Health Promotion Institute, Tehran, Iran

Purpose: Although higher levels of depressive symptoms and lower levels of sense of mastery tend to be comorbid, limited information exists on racial differences in the longitudinal associations between the two over time. The current study compared Black and White American older adults for the longitudinal links between depressive symptoms and mastery in the United States.

Methods: Using data from the Religion, Aging, and Health Survey, 2001–2004, this longitudinal cohort study followed 1493 Black (n = 734) and White (n = 759) elderly individuals (age 66 or more) for 3 years. Depressive symptoms [Center for Epidemiological Studies-Depression scale (CES-D), 8 items] and mastery (Pearlin Mastery Scale, 7 items) were measured in 2001 and 2004. Demographics, socio-economics, and physical health were covariates and race was the focal moderator. Multi-group structural equation modeling was used for data analysis, where groups were defined based on race.

Results: Among White but not Black older adults, higher levels of depressive symptoms at baseline predicted a greater decline in sense of mastery over 3 years of follow-up. Similarly among Whites but not Blacks, individuals with lower mastery at baseline developed more depressive symptoms over time.

Conclusion: Findings are indicative of Black-White differences in reciprocal associations between depressive symptoms and mastery over time. Race alters how depression is linked to changes in evaluation of self (e.g., mastery) over time.

Keywords: population groups, ethnic groups, african americans, depressive symptoms, depression, mastery, self-efficacy

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***Correspondence:**
Shervin Assari
assari@umich.edu

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INTRODUCTION

According to the Black-White health paradox, one of the mysteries of health research (Keyes, 2009; Barnes et al., 2013; Mouzon, 2013, 2014; Assari et al., 2015; Watkins et al., 2015), despite higher exposure to psychosocial and economic stress and adversities, Blacks less frequently meet criteria for depression compared to Whites (Owen, 1996; Lindhorst et al., 2007; Signorello et al., 2007; Williams et al., 2007; González et al., 2010; Cabassa et al., 2013; Jackson et al., 2013; Johnson-Lawrence et al., 2013). In line with this paradox, Blacks and Whites differ in psychosocial and health

factors that correlate with depression and depressive symptoms (Sachs-Ericsson et al., 2007; Gavin et al., 2010; Lewis et al., 2011; Barnes et al., 2013; Capistrant et al., 2013; Assari and Lankarani, 2014; Assari, 2014d; Assari et al., 2016b). This hypothesis is supported by research showing that depression increases the risk of chronic medical conditions among Whites but not Blacks (Assari et al., 2015, 2016a). Depressive symptoms predict chronic medical conditions (Assari et al., 2015) and all-cause (Assari et al., 2016a; Moazen-Zadeh and Assari, 2016) and cause-specific (Assari and Burgard, 2015) mortality among Whites but not Blacks. In another set of studies, depressive symptoms have failed to correlate with expected biological markers, such as inflammatory markers (Case, 2014; Stewart, 2016; Vrany et al., 2016).

The first possible explanation proposed by Keyes for the Black-White health paradox is that Blacks may experience some levels of growth or flourishing in the presence of adversities (Keyes, 2009). Assari has found that Blacks are systematically more resilient to the effects of psycho-social factors, which may reflect an adaptive resilience of Blacks as a result of life under economic and social adversity, or culture (Krause, 2002; Assari et al., 2016c; Assari, 2016a,b,c; Assari and Lankarani, 2016b; Assari and Dejman, 2016). These two explanations are supported by studies documenting higher availability and efficacy of interpersonal psychosocial resources, such as social support and religion, for Blacks than Whites (Lincoln et al., 2003; Keyes, 2009; Barnes et al., 2013; Mouzon, 2013, 2014; Assari et al., 2015). Jackson has suggested that Blacks use behavioral coping mechanisms that lower the risk of emotional problems, however, increase the risk of metabolic and cardiovascular conditions (Jackson and Knight, 2006; Mezuk et al., 2010, 2013).

There are also a series of methodological explanations that attribute this paradox to measurement errors or selection biases. For instance, some evidence suggests that depression measures that are designed and validated for Whites fail to capture depression in Blacks (Moazen-Zadeh and Assari, 2016). In one study, baseline depressive symptoms were predictive of the subsequent risk of Major Depressive Disorder (MDD) after 15 years among Whites but not Blacks (Moazen-Zadeh and Assari, 2016). This view is also supported by the literature suggesting lower validity of depressive measures among Blacks (Williams et al., 2007) as well as studies that depression may differently present among Blacks and Whites (Brown et al., 1996; Blazer et al., 1998; Zayas et al., 2002).

The third generation of explanations recently proposed by Assari is that depression differently influences dysfunctional attitudes about self (e.g., mastery), others, and the future (e.g., Hope) (Assari, 2016a; Assari and Lankarani, 2016a; Assari and Dejman, 2016). In this view, depression is qualitatively different among Blacks and Whites; thus Blacks and Whites may differ in the link between depression and mastery, defined as a sense of having control over the forces that affect one's life (Fok et al., 2012). We argue that high levels of psychosocial resources, such as social support and religion, may make Blacks more resistant to decline in mastery in the face of social adversities (Lincoln et al., 2003; Assari, 2013; Mouzon, 2013, 2014). Level of mastery will have implications on how stress may affect depression among Blacks and Whites (Assari and Lankarani, 2016c). This view is also supported by studies suggesting that locus of control, mastery, self-efficacy, and control over life may not have similar meanings in Whites and Blacks (Deaton and Lubotsky, 2003; Dressler et al., 2005; Dowd and Zajacova, 2007; Assari, 2014c, 2016e; Assari et al., 2016c). In a number of studies, Assari has shown that depression differently influences dysfunctional attitudes about self, others, and the future (Assari, 2016a; Assari and Lankarani, 2016a; Assari and Dejman, 2016). For instance, lower levels of these control beliefs may have more significant health consequences for Whites than Blacks (Assari, 2016c).

Built on the *differential effect hypothesis* (Assari, 2016b,d; Assari and Lankarani, 2016b; Assari and Sonnega, 2016), we conducted the current study to compare Black and White American older adults for the reciprocal longitudinal associations between depressive symptoms and mastery over time. This hypothesis is in line with what Belsky and others have called 'differential susceptibility to environmental influences' or 'differential susceptibility to the context' (Belsky, 1997; Boyce and Ellis, 2005; Belsky et al., 2007; Belsky and Pluess, 2009). Given that previous studies have shown that religion and social support may be more available and effective for Blacks compared to Whites (Krause, 2006a; Skarupski et al., 2013) paired with the finding that Blacks are more resilient to the effect of psychosocial factors (Krause, 2002; Assari, 2016a,b,c; Assari and Lankarani, 2016b; Assari and Dejman, 2016; Assari et al., 2016c), we expected to observe weaker reciprocal longitudinal links between depressive symptoms and mastery among Blacks compared to Whites. We used nationally representative data to generate results that are generalizable to the U.S. population of older adults.

METHODS

Design and Setting

With a longitudinal panel design, data came from Waves 1 and 2 of the Religion, Aging, and Health Survey, 2001–2004. The study is a 3 year follow up of a nationally representative household sample of Black and White older adults in the U.S. (Krause, 2006b, 2009).

Sampling and Participants

The study participants were either White or Black older adults. Older Blacks were over-sampled in the survey. All participants were non-institutionalized English speaking people of ages greater than 65 years. The study population was limited to those who were either Christians or those who were never associated with any faith.

Measures

Race, demographic data (age and gender), and socio economic status (education) were measured at baseline in 2001. Number of chronic medical conditions (13 chronic medical conditions) was measured in 2004. Depressive symptoms and mastery were measured in 2001 and 2004.

Depressive Symptoms

An 8–item Center for Epidemiological Studies-Depression scale (CES-D) (Radloff, 1977) was used to measure depressive symptoms in 2001 and 2004. Items measured the extent to which respondents felt depressed or had somatic symptoms. Abbreviated CES-D measures have shown acceptable reliability and similar validity as compared to the original 20–item version (Andresen et al., 1994; Zhang et al., 2012; Amtmann et al., 2014). Items used were as the following: (1) I felt I could not shake off the blues even with the help of my family and friends, (2) I felt depressed, (3) I had crying spells, (4) I felt sad, (5) I did not feel like eating, my appetite was poor, (6) I felt that everything I did was an effort, (7) My sleep was restless, and (8) I could not get going. All these items were selected from the negative domain of the CES-D; positive affect and interpersonal items were not reflected in this version of the CES-D. Item responses were 1 ("rarely or none") to 4 ("most or all of the time"). We calculated the mean score which treated depressive symptoms as a continuous measure, with a potential range from 1 to 4. Higher scores indicated more severe depressive symptoms. (Abu-Raiya et al., 2016; Hayward and Krause, 2016)

Mastery

We used seven items from the Pearlin Mastery Scale (Cairney and Krause, 2008). Items included (1) You have little control over the things that happen to you, (2) There is really no way you can solve some of the problems you have, (3) There is little you can do to change many of the important things in your life, (4) Sometimes you feel that you are being pushed around in life, (5) What happens to you in the future mostly depends upon you, (6) You can do just about anything you really set your mind to, and (7) You often feel helpless in dealing with the problems of life (Pearlin and Pioli, 2003). This construct is similar to sense of control (Wheaton, 1983; Rodin, 1986; Mirowsky, 1995, 1997). We calculated a mean score where a higher score was indicative of a greater sense of mastery (range = 0–4). Some of the items were reverse coded. The internal reliability of the scale (Cronbach's alpha) at Wave 1 was 0.94.

Number of Chronic Medical Conditions

The presence of the following chronic medical conditions were measured during the past 12 months: (1) hypertension, (2) heart problem, (3) diabetes, (4) cancer, (5) kidney disease, (6) arthritis or rheumatism, (7) intestinal disorders, (8) liver disease, (9) urinary tract disorders, (10) eye diseases, (11) any respiratory disease, and (12) any other major health problem. Possible responses included yes [1], no [0], and do not know (missing data). Number of conditions potentially ranged between 0 and 12, where a higher score was indicative of more chronic conditions. (Watkins et al., 2015) We decided to control for chronic medical conditions as physical health is correlated with mastery and depressive symptoms and may confound their link. Medical conditions may, however, be differently linked to depression based on race (MacKinnon et al., 2000; Lynch et al., 2010; Lewis et al., 2011; Barnes et al., 2013; Capistrant et al., 2013; Assari and Burgard, 2015; Assari et al., 2015).

Statistical Analysis

We used SPSS 20.0 (IBM Corp, Armonk, NY) for univariate and bivariate analyses. We used AMOS 20 (IBM Corp, Armonk, NY) for multivariable analysis. For bivariate associations, Pearson's correlations tests, independent sample *t*-tests, and paired *t*-tests were used. For multivariable analysis, we ran multi-group structural equation modeling (SEM) to test if baseline depressive symptoms and mastery predict subsequent depressive symptoms and mastery, while age, education, gender, and chronic medical conditions were controlled. We ran a multi-group model where groups were defined based on race (Kline, 2010). $P < 0.05$ was considered significant.

The Amos software computes maximum likelihood estimates in the presence of missing data (Allison, 2002; Arbuckle, 2012). Model fit was evaluated by examining the chi-square statistic, the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). A non-significant chi-square statistic, a chi-square to degrees of freedom ratio of less than 4, a CFI above 0.95, and a RMSEA value of 0.06 or less were considered as indicators of good fit (Hu and Bentler, 1999; Lei and Lomax, 2005).

RESULTS

Descriptive statistics

The study followed 1493 older adults (age 65 or greater) for 3 years. This sample included 734 Blacks and 759 Whites. Descriptive statistics overall and also based on race are shown in **Table 1**. While age was not significantly different between the racial groups, Blacks were more female, and had lower education. Blacks reported more depressive symptoms than Whites.

Multivariable Model

Our model showed an excellent fit to the data ($p = 0.468$, CMIN = 1.519, DF = 2, CMIN/DF = 0.759, CFI = 1.000, RMSEA = 0.000, 90% CI = 0.000–0.057; **Figures 1**, **2**). Depressive symptoms at baseline was associated with decline in mastery over time among Whites ($\beta = 0.10$, $p = 0.013$) but not Blacks ($\beta = 0.04$, $p = 0.369$). Mastery at baseline was also predictive of an increase in depressive symptoms over time among Whites ($\beta = 0.11$, $p = 0.007$) but not Blacks ($\beta = 0.05$, $p = 0.255$). Baseline age and gender were associated with change in depressive symptoms for Whites but not Blacks. Number of medical conditions was predictive of change in mastery and depressive symptoms among Whites and Blacks (**Table 2**, **Figures 1**, **2**).

DISCUSSION

In a nationally representative sample of older adults in U.S., we found that sense of mastery and depressive symptoms have reciprocal links among Whites but not Blacks. These Black-White differences are in line with other racial differences in psychosocial and medical correlates of depression (Sachs-Ericsson et al., 2007; Gavin et al., 2010; Lewis et al., 2011; Capistrant et al., 2013; Assari and Lankarani, 2014; Assari, 2014d; Assari and Burgard, 2015; Assari et al., 2015, 2016a,b,c; Watkins et al., 2015; Moazen-Zadeh and Assari, 2016) that collectively support the differential effect hypothesis and differential susceptibility to context.

TABLE 1 | Descriptive Statistics for the analytic sample, stratified by race and overall.

	OR	95% CI		P	OR	95% CI
	All		Whites		Blacks	
	Mean n	SD %	Mean n	SD %	Mean n	SD %
GENDER*						
Male	570	38.2	314	41.4	256	34.9
Female	923	61.8	445	58.6	478	65.1
EDUCATION						
High school diploma or higher	872	59.0	552	73.4	320	44.0
Less than High school diploma	607	41.0	200	26.6	407	56.0
	Mean	SD	Mean	SD	Mean	SD
Age	75.14	6.66	75.37	6.82	74.91	6.49
Medical conditions	1.77	1.82	1.74	1.81	1.78	1.83
Depressive symptoms *	1.49	0.69	1.47	0.62	1.52	0.77
Mastery						

*$p < 0.05$.

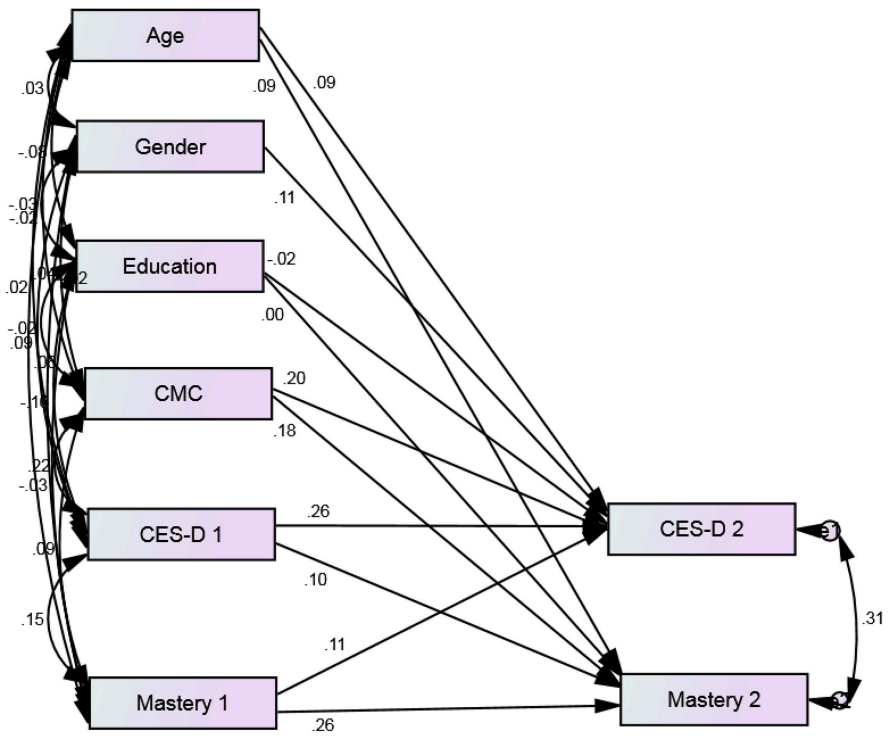

FIGURE 1 | Standardized regression weights for longitudinal associations between depressive symptoms and mastery over 3 years among White older adults from 2001 to 2004. $P = 0.468$, CMIN = 1.519, DF = 2, CMIN/DF = 0.759, CFI = 1.000, RMSEA = 0.000, 90% CI = 0 000–0.057.

These findings enhance our understanding regarding the relevance of Beck's negative cognitive triad to racially diverse groups. Based on Beck's theory, depression is a dysfunctional evaluation of self, others, and the future (Beck et al., 1990). It has been previously shown that depression and hopelessness (dysfunctional evaluation of the future) have stronger links among Whites than Blacks (Assari and Lankarani, 2016a). These findings suggest that race may alter how distorted evaluation of self, others, and the future reflects depression among populations. These findings have major clinical implications for psychotherapy and cognitive therapy of depression in diverse populations (Assari and Lankarani, 2016a).

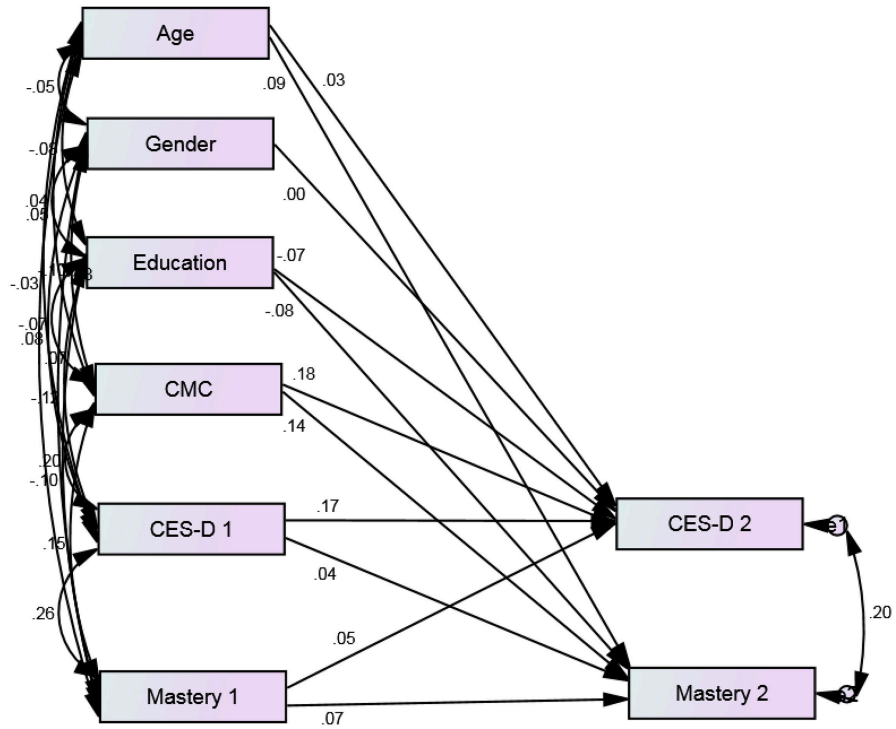

FIGURE 2 | Standardized regression weights for longitudinal associations between depressive symptoms and mastery over 3 years among Black older adults from 2001 to 2004. *P* = 0.468, CMIN = 1.519, DF = 2, CMIN/DF = 0.759, CFI = 1.000, RMSEA = 0.000, 90% CI = 0.000–0.057.

TABLE 2 | Longitudinal associations between depressive symptoms and mastery over 3 years among White and Black older adults.

			Whites		Blacks	
			B (SE)	*P*	B	*P*
W1 Depressive symptoms	→	W2 Depressive symptoms	0.26(0.05)	<0.001	0.17(0.06)	<0.001
W1 Mastery	→	W2 Mastery	0.26(0.05)	<0.001	0.07(0.05)	0.115
W1 Mastery	→	W2 Depressive symptoms	0.11(0.05)	0.007	0.05(0.07)	0.255
W1 Depressive symptoms	→	W2 Mastery	0.10(0.04)	0.013	0.04(0.04)	0.369
W1 Age	→	W2 Depressive symptoms	0.09(0.00)	0.027	0.03(0.01)	0.509
W1 Age	→	W2 Mastery	0.09(0.00)	0.025	0.09(0.00)	0.048
W1 Gender (Female)	→	W2 Depressive symptoms	0.11(0.05)	0.003	0.00(0.07)	0.942
W2 CMC	→	W2 Depressive symptoms	0.20(0.02)	<0.001	0.18(0.02)	<0.001
W2 CMC	→	W2 Mastery	0.18(0.01)	<0.001	0.14(0.02)	0.003
W1 Education (High school diploma)	→	W2 Mastery	0.00(0.05)	0.955	−0.08(0.05)	0.093
W1 Education (High school diploma)	→	W2 Depressive symptoms	−0.02(0.06)	0.648	−0.07(0.07)	0.142

P = 0.468, CMIN = 1.519, DF = 2, CMIN/DF = 0.759, CFI = 1.000, RMSEA = 0.000, 90% CI = 0.000–0.057.

Lincoln (Lincoln et al., 2003) and others (Assari, 2013; Assari, under review) have argued that social and psychological factors operate differently across racial and ethnic groups. Psychosocial processes may operate in unique manners that are distinct across each racial and ethnic group (Lincoln et al., 2003). In this view, the assumption of similarity between Blacks and Whites is the result of an absence of previous studies on race/ethnic differences, and does not have empirical evidence (Hunt, 1996; Hunt et al., 2000; Lincoln et al., 2003; McDowell, 2010; Assari, 2016c). Our findings suggest that the psychosocial processes that result in depression may depend on race.

Racial groups have unique histories, values, and cultures, which combine with life circumstances and experiences that make them differently vulnerable or resilient to risk and protective factors. In this view, the very same social factors, and the very same psychosocial theory may differently operate across all social groups (Lincoln et al., 2003). Understanding of group differences in psychosocial processes that contribute to health

and illness is essential for the promotion of health and wellbeing through altering social or psychological factors across diverse populations (Lincoln et al., 2003). This argument is core to the *differential effect hypothesis* (Assari, 2016d).

It has been shown that overall social support and support from fellow church members are stronger predictive factors against psychological distress and depressive symptoms among Blacks compared to Whites (Lincoln et al., 2003; Krause, 2006a; Assari and Burgard, 2015; Assari, under review). In 2013, Assari showed that religious (church-based) social support fully mediated the association between church attendance and overall life satisfaction for Blacks but not Whites (Assari, 2013). These are all in line with what Skarupski et al., called the Blacks' "faith advantage in health" (Skarupski et al., 2013).

Our finding adds to the existing knowledge on racial differences in the complex associations between socioeconomic status (SES), psychosocial resources (e.g., social support, coping, stress), depression, and health (Drevenstedt, 1998; Krause, 2002; Sachs-Ericsson et al., 2007; Cheng et al., 2010; Gariepy et al., 2010; Gavin et al., 2010; Cohen et al., 2012; Flegal et al., 2013; Assari, 2014a,b; Patel et al., 2014; Assari et al., 2016c). Race modifies how SES affects depression, health behaviors, and mortality (Flegal et al., 2013; Patel et al., 2014) and how depression is linked to obesity (Sachs-Ericsson et al., 2007; Gavin et al., 2010; Assari, 2014a,b), chronic medical conditions (Assari and Lankarani, 2014; Watkins et al., 2015), self-rated health (Assari, 2014d; Assari and Burgard, 2015; Assari et al., 2015), and mortality (Assari and Burgard, 2015; Assari et al., 2016a).

Race differences in vulnerabilities to the effect of risk and protective factors may be a consequence of racial differences in exposure to psychosocial risk and protective factors (Ferraro and Kelley-Moore, 2001; Lee et al., 2007; Assari and Burgard, 2015; Assari et al., 2016c), race differences in the nature of depression or mastery (Moazen-Zadeh and Assari, 2016), or racial differences in what psychosocial constructs reflect (Assari et al., 2016c). These non-specific racial differences suggest that race does not have a direct effect on health, or simply through SES, but has contextual effects that alter how resources and risk factors impact physical or mental health (Capistrant et al., 2013; Assari, 2014a,c,d, 2015; Assari et al., 2015, 2016c).

The missing link between depressive symptoms and mastery among Blacks may explain why depressive symptoms have weaker effects on self-rated health, medical conditions, and mortality among Blacks compared to Whites (Drevenstedt, 1998; Ferraro and Kelley-Moore, 2001; Dowd and Zajacova, 2007; Lee et al., 2007; Assari and Burgard, 2015; Assari et al., 2016d). In a consistent pattern, regardless of the type of the predictor, psychological variables better predict physical and mental health outcomes for Whites compared to Blacks (Ferraro and Kelley-Moore, 2001; Dowd and Zajacova, 2007; Lee et al., 2007; Assari, 2016e). These suggest higher resilience of Blacks toward different risk factors, possibly due to historical exposure to adversity.

Our findings may have implications for the elimination of racial health disparities in the US, which have existed for several decades (Deaton and Lubotsky, 2003; Dressler et al., 2005). This finding may also be relevant to the ongoing increasing trends of mortality due to mental disorders, depression, and alcohol use among White men (Case and Deaton, 2015). We believe that mastery is central to trajectories of mental disorders and chronic disease, particularly for Whites.

Our study is subject to a number of limitations. First and foremost, we measured depressive symptoms, not major depressive disorder, which would have required a structural interview. We also did not measure history of anti depressant use, which affects the course of depression. Third, we did not control for potential confounders, such as stress, religiosity, social support, and cognitive ability. Fourth, we used short versions of standard measures of mastery and depressive symptoms. Despite these limitations, this study was one of the firsts on racial differences in the links between mastery and depressive symptoms over time among older adults. Using a nationally representative sample and large sample size of Blacks can be listed as strengths of this study.

To conclude, race alters the reciprocal and longitudinal associations between depressive symptoms and sense of mastery over time. Black-White differences in the link between depression and mastery may explain why depression and depressive symptoms better predict chronic medical conditions and mortality among Whites than Blacks. Future research should test whether racial differences in the paths between depression and mastery is due to racial differences in quality of depression and control beliefs, racial differences in availability and effects of psychosocial factors (e.g., SES, religiosity, and social support) or differential salience of dysfunctional attitudes about self, others, and the future explain these differences between Blacks and Whites.

ETHICS STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants included in the study. The University of Michigan Institutional review board (IRB) approved the study protocol.

AUTHOR CONTRIBUTIONS

SA designed and analyzed this work, and contributed to revision. ML drafted and revised the paper. Both authors confirmed the last version.

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REVIEW
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Neural Correlates for Apathy: Frontal-Prefrontal and Parietal Cortical- Subcortical Circuits

Rita Moretti and Riccardo Signori*

Neurology Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

Apathy is an uncertain nosographical entity, which includes reduced motivation, abulia, decreased empathy, and lack of emotional involvement; it is an important and heavy-burden clinical condition which strongly impacts in everyday life events, affects the common daily living abilities, reduced the inner goal directed behavior, and gives the heaviest burden on caregivers. Is a quite common comorbidity of many neurological disease, However, there is no definite consensus on the role of apathy in clinical practice, no definite data on anatomical circuits involved in its development, and no definite instrument to detect it at bedside. As a general observation, the occurrence of apathy is connected to damage of prefrontal cortex (PFC) and basal ganglia; "emotional affective" apathy may be related to the orbitomedial PFC and ventral striatum; "cognitive apathy" may be associated with dysfunction of lateral PFC and dorsal caudate nuclei; deficit of "autoactivation" may be due to bilateral lesions of the internal portion of globus pallidus, bilateral paramedian thalamic lesions, or the dorsomedial portion of PFC. On the other hand, apathy severity has been connected to neurofibrillary tangles density in the anterior cingulate gyrus and to gray matter atrophy in the anterior cingulate (ACC) and in the left medial frontal cortex, confirmed by functional imaging studies. These neural networks are linked to projects, judjing and planning, execution and selection common actions, and through the basolateral amygdala and nucleus accumbens projects to the frontostriatal and to the dorsolateral prefrontal cortex. Therefore, an alteration of these circuitry caused a lack of insight, a reduction of decision-making strategies, and a reduced speedness in action decision, major responsible for apathy. Emergent role concerns also the parietal cortex, with its direct action motivation control. We will discuss the importance of these circuits in different pathologies, degenerative or vascular, acute or chronic.

Keywords: apathy, frontal cortex, striatum, parietal lobe, nucleus accumbens, anterior cingulate cortex

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****Correspondence:***
Rita Moretti
moretti@units.it

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INTRODUCTION

The clinical importance of apathy is more and more amplified in neuro-pathological context, especially and at the moment, related specifically to frontal-subcortical circuit alteration (Starkstein et al., 1992; Duffy, 2000; Aarsland et al., 2001; Starkstein and Leentjens, 2008; Massimo et al., 2009; Chase, 2011; Moretti et al., 2012). The overt definition of apathy is that of a reduced motivation, which directly involve the goal-directed behavior (Duffy, 2000) with a diminishment of emotional involvement, and difficulty in the beginning of new actions (Duffy, 2000).

Apathy is a widespread condition, in many neurological pathology, whose recognition might be helpful for dedicated therapy (Hoehn-Saric et al., 1990; McConnell et al., 1996; Campbell and Duffy, 1997; Castellon et al., 1998; Kant et al., 1998; Diaz-Olavarrieta et al., 1999; Okada et al., 1999; Cummings, 2000).

If not entirely accepted, there are many different categorization of apathy; one of the most anatomical and patho-physiological is the one, proposed (Duffy, 2000) in which different anatomical networks are involved: therefore, Duffy (2000) proposed the terms of cognitive apathy, as the one caused by an alteration of the dorso-frontal cortex, and which brings to dyseexecutive alteration; of motor apathy (Duffy, 2000) with an alteration of motor speedness and execution, mainly related to the extra-pyramidal disrupted circuits(Duffy, 2000); of cortical-sensory apathy (Duffy, 2000), due to altered teleceptive process, and therefore causing the inability to motivate and act as a consequence of sensory stimuli; and of emotional apathy(Duffy, 2000), due to an incapacity to employ the inner planning and voluntary stimulus to act with a defined aim, for a disorder of the extended region of the amygdala (Marin, 1997a,b; Duffy, 2000).

Robert et al. (2009) proposed novel diagnostic criteria for apathy which have been most widely used in recent studies. These can be summarized as lack of motivation associated with lack of:

1. Goal-directed behavior;
2. Goal-directed cognitive activity;
3. Spontaneous or reactive emotional expression, frequently characterized as "emotional blunting."

In more recent days, Quaranta et al. (2012) connected the occurrence of apathy to damage of prefrontal cortex (PFC) and basal ganglia (Chase, 2011), and define it as:

1. Emotional apathy (associated with damages of ventral striatum and orbitomedial PFC behavior form of FTD bvFTD; Quaranta et al., 2012);
2. Cognitive apathy (correlated with an impairment of the lateral PFC and dorsal caudate nuclei; Quaranta et al., 2012);
3. Deficit of auto-activation (Quaranta et al., 2012; derived from the bilateral lesions of the dorsomedial portion of PFC, the internal portion of globus pallidus, or bilateral paramedian thalamic lesions; Marin et al., 1991; Marin, 1996; Levy and Dubois, 2006; Peters et al., 2006; Zamboni et al., 2008; Chow et al., 2009; Moll et al., 2011).

As far as we have above reported, there are many different possible systematic categorization for apathy, but, at the moment, there is not an adequate and world- accepted gold-standard scale to measure apathy; in particular, there are many shortcomings of the different existing scale, due to the fact that some are heavily standing on caregivers, some other consider apathy in the context of different other neuropsychiatric events (Loewenstein et al., 2001; Njomboro and Deb, 2012; Cummings et al., 2015a,b). What it is strongly recommended is that the clinician should evaluate apathy inside the clinical behavior and cognitive status of the patient, and even in his environment situation (Duffy, 2000).

What Do We Know from Animal Experiments and Single Case Studies

The frontal-subcortical circuitry provides a unifying framework for understanding apathy (Alexander, 1994; Litvan, 2001; Monchi et al., 2006; Bonelli and Cummings, 2007).

Alexander et al. (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990; Alexander, 1994) proposed that the basal ganglia and thalamus are intimately related to frontal cortex and the inside of subcortical-frontal networks, in five parallel circuits (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990; Alexander, 1994). Two of these circuits influence the skeletal motor executive function and the ocular-motor areas.

The other three loops connect the basal ganglia and thalamus to the dorsolateral prefrontal cortex the lateral orbitofrontal cortex and the anterior cingulate/medial orbitofrontal areas (Alexander et al., 1986, 1990; Alexander and Crutcher, 1990; Alexander, 1994). The areas are involved in executive functions, attention, working-memory, focusing attention, and judgment (Fielding et al., 2006; Bonelli and Cummings, 2008). PET and fMRI imaging publications confirmed *in vivo* these models (Postuma and Dagher, 2006; Bonelli and Cummings, 2007).

The topical organization of the prefrontal cortex network is strongly reflected in the dynamic development of prefrontostriatal regions of connections (Yeterian and Van Hoesen, 1978; Yeterian and Pandya, 1991; Flaherty and Graybiel, 1993; Lattery et al., 2001; Bonelli and Cummings, 2007). The striatum recombined the information derived from the cortex to form small and specialized areas (Divac et al., 1967; Johnson et al., 1968; Divac, 1972; Brown, 1992; Lichter and Cummings, 2001; Hirata et al., 2006).

The two motor circuits (Lehericy et al., 2006) send impulses directly toward the putamen, then to ventrolateral globus pallidus internal (GPi), globus pallidus external (GPe), and caudolateral SN. The globus pallidus (GP) connects to the ventrolateral, ventral anterior, and centromedianum nuclei of the thalamus, which send projections directly to the supplementary motor area, premotor cortex, and motor cortex, completing this way the circuit.

There are three other circuits, which starts from BG and arrives to frontal areas, which are behaviorally relevant:

A dorsolateral-prefrontal circuit, which seems involved in executive functions (Alexander and Crutcher, 1990; Alexander et al., 1990; Alexander, 1994);

An anterior cingulate circuit, involved in motivational mechanisms (Alexander and Crutcher, 1990; Alexander et al., 1990; Alexander, 1994);

An orbitofrontal circuit, with lateral and medial sections. The medial part permits integration of visceral-amygdalar functions with the internal state of the organism; the lateral portion is involved with transformation of limbic and emotional information into contextually appropriate behavioral responses (Alexander and Crutcher, 1990; Alexander et al., 1990; Alexander, 1994).

Each circuit has two pathways:

1. Direct pathway, featuring a monosynaptic link between the GPi-SN pars reticulata (SNr) complex;

2. Indirect pathway, projects from striatum to GPe, connecting to the Gpi-SNr complex via the subthalamic nucleus (STN; Alexander and Crutcher, 1990; Alexander et al., 1990).

Both direct and indirect circuits project to the thalamus.

Although, each frontal-subcortical circuit constitutes a closed loop of anatomically segregated dedicated neurons, "open"-loop elements are incorporated into their functional connectivity, including parietal cortex, thalamic nuclei, prestriate cortex, and amygdala nuclei (Groenewegen and Berendse, 1990; Parent, 1990; Weinberger, 1993; Salmon et al., 2001; Bonelli et al., 2006; Bonelli and Cummings, 2007).

The dorsolateral prefrontal circuit begins in the cortical regions of areas 9 and 10, projects to the caudate nucleus (Selemon and Goldman-Rakic, 1985), via the direct pathways to the lateral faces of the GPi and SNr (Parent et al., 1984). The indirect pathway project to the dorsal GPe, and subsequently to the lateral STN (Smith and Bolam, 1990). Neurons from the lateral STN send afferents to the GPi-SNr complex. The output efferents from the basal ganglia project directly to the mediodorsal and ventral anterior thalamus (Kim et al., 1976; Illinsky et al., 1985), and return to Brodmann's areas 9 and 10 (Kievit and Kuypers, 1977; Giguere and Goldman-Rakic, 1988), relating these circuits to executive function. The prefrontal cortex can be considered as the most developed cortical site for the control and the correct operative selection of executive functions and appropriate behavior (Kolb et al., 2004; Nácher et al., 2006; Alexander and Brown, 2011). As pointed out by Leal-Campanario et al. (2013) it seems more precise to better define the prefrontal cortex into the dorsolateral part, which seems to be tightly bound to the working memory and to the correct operative choice of appropriate behavior, and the medial prefrontal area, which appears to guarantee the emotional color of intentional action and of the acquired act, including for animals and humans, as perfectly stated by Leal-Campanario et al. (2013) "associative conditioning" (Weiss and Disterhoft, 2011; Jurado-Parras et al., 2012). Studies based on transcranial magnetic stimulation support the hypothesized role of the prefrontal cortex (Petrosini, 2007) and experimental data extend it toward its projection on nucleus accumbens (Jurado-Parras et al., 2012) in imitative learning in humans. To become even more precise, the caudal medial prefrontal part participate in the gaining, and in the recovery of the conditioning (Simon et al., 2005), whereas the rostral medial part restrains the conditioned act sequence, without limiting its acquisition (Leal-Campanario et al., 2007, 2013). To the rostral part of the medial dorsal prefrontal cortex widely projects the mediodorsal thalamic nucleus (Leal-Campanario et al., 2007, 2013) and diffuse projections from it and arrives to the anterior cingulate cortex (ACC), exerting on it an inhibitory effect, but also suggesting that the effects of this area is not constant and univocal, but it acts as an ongoing control system, decreasing or increasing the operative execution of a conditioned response, in relation to environment, time, and occurrence. In fact, what clearly merge from another important study (the rostral medial prefrontal cortex inhibits the execution of the reflexed motor act, evoking what Leal-Campanario et al., 2007) defined as "a freezing behavior," but rather curiously, this marked inhibition to-act system does not reduce the possibility to acquire different conditioned response. On the contrary, when there is a cortical depression of this area, the animal can act more rapidly in response to a condition stimulus (Weiss and Disterhoft, 2011; Leal-Campanario et al., 2013).

This ongoing control process is exerted directly from the discharge of the rostral medial part of prefrontal cortex, but highly supported by its diffuse projections to caudate, and claustrum and via these nuclei to the basal ganglia, mediodorsal thalamic nuclei, as above mentioned, and to midline thalamic nuclei, highly related to the process of arousal, selective attention, but also to the substantia nigra pars reticulate, fundamental for motor action incipit (Basso and Evinger, 1996; Kronforst-Collins and Disterhoft, 1998; Siegel et al., 2012; Leal-Campanario et al., 2013), to the superior colliculus and to pontine nuclei (Kronforst-Collins and Disterhoft, 1998; Fuster, 2001; Siegel et al., 2012).

The orbitofrontal circuit begins in the lateral orbital gyrus of area 11 (Mega and Cohenour, 1997; Mega et al., 1997) and in the medial inferior frontal gyrus of the areas 10 and 47 in humans (Mega and Cohenour, 1997; Mega et al., 1997), send projections to caudate, then to the SNr and to GPi (Johnson and Rosvold, 1971). The caudate is the start point of an indirect loop (Smith et al., 1990), which passes through the dorsal GPe, the STN side, and reaches GPi and SNr (Smith et al., 1990). Neural networks from the GP and SN to the mediodorsal thalamus and ventral anterior thalamus (Illinsky et al., 1985; Selemon and Goldman-Rakic, 1985) complete the neural loop into the lateral orbitofrontal cortex (Illinsky et al., 1985).

There is another division of this circuit that has been identified by various studies (Mega and Cohenour, 1997; Mega et al., 1997): the fibers originate from inferomedial prefrontal cortex, and the medial orbital gyrus of area 11 (Mega and Cohenour, 1997; Mega et al., 1997) and project to the accumbens, to medio-ventral pallidum; they arrive into the mediodorsal thalamic nucleus, and to conclude the loop arrive in the medial orbitofrontal cortex (Mega and Cohenour, 1997; Mega et al., 1997). This portion of the cortex has reciprocal relations with the magnocellular division of the accessory basal amygdala (Mega and Cohenour, 1997; Mega et al., 1997). The orbitofrontal inferomedial cortex has many other ways of connecting with the rostral insula, and Brodmann's areas 24, 25, 32 (infracallosal cingulate areas), and 38, regions that are part of the ACC (Johnson and Rosvold, 1971; Mega and Cohenour, 1997; Mega et al., 1997). The orbitofrontal cortex receives inputs from the limbic system (Lichter and Cummings, 2001) and participate in the awareness, in the insight, in the appropriate, and predefinite social conduct (Eslinger and Damasio, 1985; Starkstein and Kremer, 2001). In fact, ACC is the trait d'union between area 24 and the ventromedial caudate, putamen, nucleus accumbens, and olfactory tubercle (Selemon and Goldman-Rakic, 1985), originally defined as the limbic striatum (Levy and Dubois, 2006); from these nuclei the fibers arrives to the GPi and GPe(Lichter and Cummings, 2001) and to SN (Critchley, 2005). Now, the connection system, at this point, departs from GPe and arrives to STN, which directs to the ventral pallidum (Leal-Campanario et al., 2013), from that point via the mediodorsal thalamus (Critchley, 2005) and conclude the loop into the anterior ACC (Goldman-Rakic and Porrino, 1985).

Two clinical conditions have been related to lesions in these regions.

The first one is the "Akinetic mutism," clinically related to a lesion of the anterior cingulate, either unilaterally, either bilaterally (Ackermann and Ziegler, 1995; Mega and Cohenour, 1997; Mega et al., 1997; Oberndorfer et al., 2002). Akinetic mutism is a dramatic clinical condition where the human being is apathic, totally deprived of motivation, absent of primary stimuli, such as hunger, psycho-motor initiative, lack of verbalization, and inability to answer questions or commands (Goldman-Rakic and Porrino, 1985; Ackermann and Ziegler, 1995; Mega and Cohenour, 1997; Mega et al., 1997; Oomman and Madhusudhanan, 1999; Anderson et al., 2003; Tengvar et al., 2004).

The second one is apathy, driven out by bilateral lesions of ventrolateral and dorsomedial thalamic nuclei (Bogousslavsky et al., 1988; Levy and Dubois, 2006), GP and the internal capsule (Helgason et al., 1988; Starkstein et al., 1993), the ansa lenticularis (internal pallidal, posterior limb of the internal capsule, and end in the peduncolopontine nucleus; Bechara and van der Kooy, 1989; Bhatia and Marsden, 1994; Ackermann and Ziegler, 1995). We can induce a syndrome similar to akinetic mutism injecting 6-hydroxy dopamine in the SN, ventral tegmental area, or nigrostriatal tract within the medial forebrain bundles of the lateral hypothalamus (Ungerstedt, 1970, 1971). Administration of apomorphine (a direct dopamine agonist) could reverse behavioral deficits (Ungerstedt, 1971; Marshall and Ungerstedt, 1976) and a pretreatment with spiroperidol (a dopamine receptor antagonist), could block them (Marshall and Gotthelf, 1979).

Confirmation of these observations came from the case of a patient who developed akinetic mutism due to surgical removal of a tumor of the anterior hypothalamus who responded to treatment with lergotrile and bromocriptine (dopamine receptor agonists), but not to carbidopa/L -dopa or methylphenidate (presynaptic dopamine mimetics; Ross and Stewart, 1981). This case suggested that the base of akinesia and apathy lies on a direct loss of dopaminergic input to the cingulate or other corticolimbic structures rather than to the striatum (Nemeth et al., 1986; Echiverri et al., 1988; Combarros et al., 2000; Alexander, 2001).

As with akinetic mutism, even for apathy, it was observed a substantial response to treatment with dopamine-agonists, suggesting a common role of dopaminergic pathways in both conditions (Marin et al., 1995; Watanabe et al., 1995; Lichter and Cummings, 2001). Apathy that appears in experimental models of Alzheimer's disease can be also interpreted as an alteration of cholinergic disconnections of structures of the ACC, e.g., basal nucleus of the amygdala (Mega and Cohenour, 1997; Mega et al., 1997), and the paramedian thalamic portions, probably for their intrinsic role of connecting basal forebrain to the ARAS system, deriving from the cholinergic pedunculo-pontine projections.

To summarize, we can detect a theoretical model for the Neural Substrates of Motivation traced out by Kalivas: (Kalivas et al., 1994)

Subcircuit number 1 (Kalivas et al., 1994): this circuit is mediated by a loop via the ventral tegmentum, through the nucleus accumbens and to the ventral pallidum. As Kalivas pointed out, this circuit gives motivation to the operative process, in the "motivational working memory" (Kalivas et al., 1994).

Subcircuit number 2 (Kalivas et al., 1994): this circuit is composed by the ventral pallidum, the medial dorsal nucleus of the thalamus, the prefrontal cortex, the nucleus accumbens, and the ventral tegmentum. As Kalivas (Kalivas et al., 1994) underlined this network provides "the cognitive coloring of motivation" (Kalivas et al., 1994).

Subcircuit number 3 (Kalivas et al., 1994): this circuit is composed by the projections via the ventral pallidum, the pedunculo-pontine nucleus and the ventral tegmentum, and strengths the passage from the arousal into motivation (Kalivas et al., 1994).

Subcircuit number 4 (Kalivas et al., 1994): this circuit occurs between the ventral tegmentum and nucleus accumbens, via the amygdala and implements the "reward memory into motivational response" (Kalivas et al., 1994).

Dopamine is the principal neurotransmitter of the four dopaminergic systems; nigro-striatal, mescortical, meso-limbic, and tubero-infundibular vias. Dopamine subserves various system, in particular concerning the arousal, the motor refinement system, the goal-motivation (Duffy, 1997a,b, 2000).

The cholinergic network is a widespread system, which originates form the Meynert nucleus, participate to the ARAS system, which arrives to the mesencephalic and tectal region, the limbic system, regulates the extrapyramidal nigro-striatal dopaminergic system, the thalamic nuclei, and basal forebrain. Therefore, cholinesterase and butyrrilcholinesterase inhibitors have been employed for apathy therapy (Hoehn-Saric et al., 1990; Duffy, 2000).

Serotonin, a part from the mood and pain modulation regulatory system, via raphe magnum and frontal projections, has an intrinsic activity on enhancing the dopamine networks of the ventral tegmentum and nucleus accumbens (Duffy, 2000) via the 5-HT3 receptors, reinforcing therefore motivational tenor (Kalivas et al., 1994; Duffy, 2000) (Supplementary Material).

WHAT DO WE KNOW ABOUT APATHY FROM CLINICAL PRACTICE?

Apathy is common in distinct neurological disorders. There are no authoritative estimates available on the prevalence of apathy in general, but it has been estimated that ∼10 million people in the US suffer from apathy (Chase, 2011; Clarke et al., 2011; van Dalen et al., 2013). Across various disorders, apathy is regarded as the strongest predictor of poor cognitive, functional, and occupational outcome, reduced medication compliance, increased caregiver burden, diminished quality of life, and general health (Levy et al., 1998; Stuss et al., 2000; van Reekum et al., 2005; Guimaraes et al., 2008; Dujardin et al., 2009; Ishii et al., 2009; Starkstein et al., 2009; Jorge et al., 2010; Benoit and Robert, 2011; Chase, 2011; Clarke et al., 2011; Kostic and Filippi, 2011; Hsieh et al., 2012; Caeiro et al., 2013; Moretti et al., 2013; Santangelo et al., 2013; van Dalen et al., 2013; Stella et al., 2014; Theleritis et al., 2014; Fervaha et al., 2015; McIntosh et al., 2015).

Apathy Following Cerebrovascular Accidents

Many data seem to forewarn the clinician that a patient with CVS may develop an apathy syndrome (which has been defined as a Post-Stroke-Apathy, PSA; Brown and Pluck, 2000). Tatemichi et al. (1992) postulate that stroke lesions to the posterior limbs of internal capsule disrupt the major outflow tract of the internal pallidum, the ansa lenticularis, which connects to the mesencephalic locomotor region (MLR), critical in generating goal-oriented behavior (Tatemichi et al., 1992; Kos et al., 2016). Okada et al. (1997) reported that apathy is related to reduced cerebral blood flow in the right dorsolateral frontal and left frontotemporal regions (Duffy, 2000; Hama et al., 2007).

Stroke patients with apathy showed more right-sided lesions in general, and specifically more white- matter hyperintensities within the right fronto-subcortical circuit (Okada et al., 1997; Brodaty et al., 2005; Caeiro et al., 2012), to higher amount of perventricular white matter hyperintensities (Finset and Andersson, 2000), lower fractional anisotropy values (FA) in the anterior corona radiata and right inferior frontal gyrus (Tang et al., 2013), and an increased number of microbleeds (Yang et al., 2015). In a DTI connectivity analysis in stroke patients by Yang et al. (2015) an "apathy-related sub-network" merged in relation with apathy: the right supra-marginal gyrus, right precuneus, and right paracentral lobule, the right superior temporal gyrus, bilateral insula (Yang et al., 2015), the hippocampus, right putamen, right thalamus, and posterior cingulum (Yang et al., 2015).

Within a study focusing apathy due to subcortical lesions, regional changes at a distal location from the lesion site were reported, namely in the posterior cingulate cortex (Tatemichi et al., 1992; Deguchi et al., 2013; Matsuoka et al., 2015), bilateral basal ganglia damage (Levy et al., 1998; Moretti et al., 2013), isolated pontine or cerebellar infarcts (Piamarta et al., 2004; Hoffmann and Cases, 2008; Onoda et al., 2011).

Alzheimer's Disease

Alzheimer's disease (AD) affects memory and cognition, but all AD patients develop neuropsychiatric symptoms (NPS; Lyketsos et al., 2000, 2002; Steinberg et al., 2008; Onoda and Yamaguchi, 2011), including apathy (Marin et al., 1991; Robert et al., 2009). NPS is the most important cause of increase of caregiver'stress, but there is no general concordance or FDA-approved medications for NPS in AD (Sultzer et al., 2008; Rosenberg et al., 2013; Porsteinsson et al., 2014; Peters et al., 2015).

An important study by Benoit et al. (1999) demonstrated that apathy but not depressed patients had significantly lower scores on cognitive tests (Porsteinsson et al., 2014).

Ample epidemiological data indicate, on the other hand, that in AD, individual NPS rarely occur alone (Hoffmann and Cases, 2008). While, these groupings have been supported by limited studies (Jonsson et al., 2010; Geda et al., 2013) others do not support this approach (Jeste and Finkel, 2000; Olin et al., 2002; Robert et al., 2009; Trzepacz et al., 2013; Cummings et al., 2015a,b). Data, therefore, might be confused and not unequivocal at all. Many data established a possible link between apathy and AD with a decreased reliability of ACC network, mainly due to an increased generalized amyloid depositions (Canevelli et al., 2013), a volume loss in ACC (Apostolova et al., 2007; Bruen et al., 2008; Marshall et al., 2013; Stanton et al., 2013), a decreased perfusion in ACC (Benoit et al., 2004; Lanctôt et al., 2007; Tunnard et al., 2011), a decreased ACC white matter related integrity (Robert et al., 2006; Kim et al., 2011; Hahn et al., 2013), and increased amyloid burden in right ACC (Ota et al., 2012; Mori et al., 2014). Apathy is also associated with decreased posterior cingulate (PCC metabolism; Migneco et al., 2001), with a reduced insular volume (Moon et al., 2014a; Delrieu et al., 2015), and with decreased inferior temporal cortical (ITC) thickness (Moon et al., 2014b; Guercio et al., 2015), with cortical shrinkage of the frontal cortex (Apostolova et al., 2007; Bruen et al., 2008; Marshall et al., 2013; Stanton et al., 2013), with greater amyloid burden in bilateral frontal cortex (Ota et al., 2012), reduced orbitofrontal metabolism on the left (Donovan et al., 2014) or right (Benoit et al., 2004), and reduced connectivity in left-sided functional connectivity, with thalamus and parietal cortex, and amygdala (Holthoff et al., 2005; Kang et al., 2012; Ota et al., 2012; Baggio et al., 2015). Galantamine, as a cholinesterase inhibitor has been linked to a slower decrease of the putamen metabolism (Zhao et al., 2014), based on FDG-PET study (Zhao et al., 2014). One neurochemical study of CSF in apathy-patients suffering from AD (Mega et al., 2005) demonstrated an higher levels of phospho-tau, related to advanced neurdegenerative process (Skogseth et al., 2008).

Using 99 m-Technetium SPECT cerebral blood flow (CBF) abnormalities were found in bilateral frontal regions: negative correlations were found between apathy and orbitofrontal regions (Benoit et al., 2004; Skogseth et al., 2008), right inferior frontal (Jack et al., 2013), and the right and bilateral medial (Jack et al., 2013; Baggio et al., 2015), and dorsolateral regions, right lingual gyrus (Craig et al., 1996; Benoit et al., 2002; Robert et al., 2006), right posterior temporo-parietal area (Schroeter et al., 2011).

Mori et al. (2014) investigated amyloid-B (AB) deposition using ((11)C) Pittsburgh Compound-B (PiB) PET in relation to apathy in AD: elevated levels of AB are seen (Mori et al., 2014) throughout the whole frontal cortex, bilateral insula, and right ACC.

AD patients white matter alterations related to apathy have been investigated (Kostic and Filippi, 2011). Often DTI is used to evaluate white matter integrity, as quantified with fractional anisotropy (FA). In patients with high apathy, lower FA values were found within the left, right, or bilateral anterior and posterior cingulum, the genu, body, and splenium of the corpus callosum (Holthoff et al., 2005; Hahn et al., 2013; Baggio et al., 2015).

Furthermore, diffusion abnormalities in the right thalamus and parietal regions were associated with higher apathy (Mori et al., 2014; Kang et al., 2012). Data are not univocal (Donovan et al., 2014; Delrieu et al., 2015). One fMRI study found alterations in functional limbic-hypothalamic networks in relation to apathy (Tatemichi et al., 1992; Starkstein et al., 1997; Balthazar et al., 2014).

Furthermore, one study that included both AD and Lewy body disease patients, investigated the relationship between apathy and striatal dopamine uptake, using (123)I-FP-CIT SPECT (Aalten et al., 2008): higher apathy was associated with a reduced dopaminergic binding potential in the right putamen (Aalten et al., 2008). On the other hand, another study reported no association with D2/D3 dopamine receptor density (David et al., 2008; Reeves et al., 2009; Cuthbert and Insel, 2013; Grupe and Nitschke, 2013; Rosenberg et al., 2013).

In our opinion, two of the most significant studies which start form the observation that AD patients did not frequently show isolated NPS symptoms, and that overlap networks should be taken into account are below reported.

Rosenberg et al. (2013) hypothesized, that apathy is one of the many different coexistent behavior symptoms in AD, and therefore these symptoms correlate with a dysfunction in several structures such as ACC, orbitofrontal cortex, and insula, as well as amygdala and striatum. As stated by Grupe and Nitschke (2013), apathy might be the behavior response toward the anxiety-provoking situations, which might be very normal and daily living activity, but inducing apprehension in AD patients (Grupe and Nitschke, 2013). Therefore, in AD one can observe an altered balance mechanism, which alterantively regulates apathy or anxiety.

Parkinson's Disease

The very first study on apathy and neurodegenerative pathology concerns Parkinson's Disease (PD): Starkstein et al. (1992) reported that in PD patients apathy is a serious problem, related to greater cognitive impairment, and to depletion of catecholamines in the locus ceruleus. Another clinical study reported that apathy tended to cluster with anxiety, whereas hallucinations, delusions, and irritability formed another distinct behavioral cluster (Insel et al., 2010). There are not adequate existamated prevalence of apathy in PD, arising up to 51% of the entire PD population (Duffy, 2000; Stuss et al., 2000; Starkstein et al., 2009), depending on the assessment and also deriving form not universally considered inclusion/exclusion criteria (Levy et al., 1998; Stuss et al., 2000; Starkstein and Leentjens, 2008; Starkstein et al., 2009; Moretti et al., 2013; many studies included patients with super-imposition of AD with parkinsonism (Stuss et al., 2000; Starkstein and Leentjens, 2008; Dujardin et al., 2009; Starkstein et al., 2009). Starting from the anatomical consideration of dopaminergic pathways, all the four dopaminergic mainstreams, the nigro-striatal, the meso-limbic, the meso-cortical, and the tubero-infundibular dopaminerg can somehow been involved in apathy determination in PD patients (Ljungberg and Ungerstedt, 1976; Insel et al., 2010; Cuthbert and Insel, 2013). But apathy in PD does not seem dependent on the duration of the disease, the severity of symptoms and the dosage of Levodopa; everything indicates that the brain changes that lead to apathy in Parkinson's disease are different from those involved in the apathy associated with motor symptoms (Levy et al., 1998; Dujardin et al., 2009; Moretti et al., 2013). Apathy and depression are quite divided symptoms, with a prevalence of depression than apathy in progressive supranuclear palsy (Insel et al., 2010; Cuthbert and Insel, 2013) of apathy in corticobasal degeneration (Levy et al., 1998; Litvan et al., 1998; Aarsland et al., 1999; Moretti et al., 2013).

Considering the specific information deriving from neuroimaging, apathy in PD has been studied (Tatemichi et al., 1992).

Reijnders et al. (2010) found an association between higher apathy and lower gray matter density values with voxel based morphometry analyses, in the bilateral inferior parietal gyrus, and right precuneus (Reijnders et al., 2010). Skidmore et al. (2013) investigated functional integrity of the brain in relation to apathy by using voxel-wise fractional amplitude of low frequency fluctuations analysis in resting state fMRI data: apathy was best predicted by a lower signal amplitude in the right middle orbitofrontal cortex and bilateral subgenual cingulate cortex, in the left supplementary motor cortex (SMA), the left inferior parietal lobule, and left fusiforme gyrus (Robert et al., 2012; Skidmore et al., 2013). According to the review by Kos et al. (2016) multiple fluorodeoxyglucose (FDG-) PET-studies specifically found a positive correlation of apathy and cerebral metabolism during rest in the right middle frontal gyrus, right inferior frontal gyrus, left anterior insula (Skidmore et al., 2013), bilateral orbitofrontal lobes, and bilateral anterior cingulate (Robert et al., 2012), and left posterior cingulate cortex (Huang et al., 2013), an increased cerebral metabolism in the right cuneus (Skidmore et al., 2013) and reduced metabolism within the right inferior parietal lobe and left superior temporal gyrus (Robert et al., 2012). Functional connectivity within the striatum and between striatal and ventrolateral prefrontal regions was more impaired in patients with high apathy compared to low (Holthoff et al., 2005). Data are not univocal, since two other studies (Robert et al., 2009, 2014) did not find out any structural differences when comparing apathetic to non-apathetic PD patients.

As strongly pointed out by Kos et al. (2016), it has been found an inverse correlation between catecholaminergic binding potential, indicative of a specific loss of dopamine and noradrenaline innervation and apathy, in the bilateral ventral striatum in resting-state analysis (Isella et al., 2002).

Subcortical Vascular Dementia

Subcortical vascular dementia (sVaD) relates to small-vessel disease (Remy et al., 2005) and encompasses small vessel arteriosclerosis, liphyalinosis and arteriosclerosis (Remy et al., 2005), resulting in lacunar infarct occurring in distribution of small arterioles, usually in the white matter, basal ganglia, thalamus, and pons (Roman et al., 1993; Remy et al., 2005; Jelinger, 2013). Due to the anatomical disposition, sVAD include a systemic progressive dysexecutive syndrome, and apathy (Chui, 2001; Dujardin et al., 2009; Moretti et al., 2015). Starkstein et al. (2009) observed that in patients who experienced apathy in combination with depression, more white matter hyperintensities were found in the parietal lobes compared to patients without apathy and depression or in groups with apathy or depression only [see data and comments in Kos et al. (2016)]. Neuropathological data here lacks, but can be resumed from other studies.

Guimaraes et al. (2008) adapted a pathophysiological model for apathy in AD, for sVAD: ACC and OFC (involved in goal—motivated planned action) via the basolateral amygdala and nucleus accumbens, projects to the ascending frontostriatal pathway and to the dorsolateral prefrontal cortex (PFC), fundamental for the executing correct behavior (Guimaraes et al., 2008). Damage to the ACC and OFC leads to apathy (Guimaraes et al., 2008): the same result might be derived from the damage of the connecting subcortical vias, from BG to ACC and OFC (Guimaraes et al., 2008). In our opinion (Chui, 2001; Dujardin et al., 2009), we suggest a putative role for the subcortical networks in connection with the pars triangularis, the superior frontal gyrus, and the orbital operculum and may suggest that degeneration of the neural networks toward OFC and ACC can be associated to apathy, as the same result, via different pathway (Chui, 2001; Dujardin et al., 2009). Recently, white matter hyperintensities in the frontal cortical and subcortical areas have been associated with apathy (McIntosh et al., 2015), not confirmed by another study (Pluck and Brown, 2002). Behavior alterations and white-matter lacunes of basal ganglia in AD resulted in a two- to three-fold increased risk of delusions, apathy, hallucinations, and depression (Rosen et al., 2005).

Even if there are very few, and limited cases of sVAD neuroimaging dedicated study for the correlation between apathy and white matter burden, we can deduct some information in the AD patients with white matter alterations and apathy (Kos et al., 2016). In patients with high apathy, lower FA values were found within the left, right, or bilateral anterior and posterior cingulum (Ott et al., 1996; Robert et al., 2006; Kang et al., 2012; Hahn et al., 2013), with non-specific white matter changes (Tighe et al., 2012; Geda et al., 2013) and with additional increment of white matter hyper- intensities in the frontal lobes (Starkstein et al., 2009) and basal ganglia (Baggio et al., 2015), of the right thalamus and parietal regions (Kang et al., 2012). New dedicated studies should take sVAD and apathy as the principal focus of neuroimaging detection.

CONCLUSIVE STATEMENT

Apathy is a widespread condition, which definitively increment the burden of the basal predisposing neurological conditions; there are, at the moment, not adequate clinical instrument, to evaluate it.

What do we know form animal models (Watanabe et al., 1995) is that apathy should be subserved by four different circuits, which mediates the motivational working memory, the cognitive coloring of motivation, the integration of arousal into motivation, and the reward memory into motivational response.

The information which derived from *in vivo* clinical practice do not object and refuse these circuits.

Kos et al. (2016) and Tatemichi et al. (1992) review confirms the association between abnormalities within the fronto-subcortical circuitry and apathy. In addition, this review highlights the involvement of the ACC and adds the inferior parietal cortex as a region of interest (Kos et al., 2016; Guimaraes et al., 2008; Chui, 2001; Moretti et al., 2015), relating ACC and parietal cortex in motivation and reward systems (Tekin and Cummings, 2002; Carrera and Bogousslavsky, 2006; Palmqvist et al., 2011; Rochat et al., 2013; Blundo and Gerace, 2015).

Wide neural networks support apathy: the medial frontal regions and the dorsolateral prefrontal cortex (DLPFC), the so-called "executive circuit" supports the ability to generate and maintain purposeful, goal-directed behavior (Dujardin et al., 2009; Quaranta et al., 2012). The inferior parietal cortex, described primarily by Litvan (Aarsland et al., 1999), in cortico-basal degeneration patients, where apathy is much more common than in PSP or PD [data confirmed in Moretti et al. (2005) (Hoffstaedter et al., 2013; Westerholz et al., 2014)], is involved too. By means of fMRI, the inferior parietal cortex (Westerholz et al., 2014) increased activation (among other regions in the fronto-subcortical network) during self-initiated movements and goal-directed behavior in a healthy sample (Jenkins et al., 2000; Desmurget and Sirigu, 2009; Westerholz et al., 2014; Kos et al., 2016).

Impairments in the generation of ideas for possible actions may lead to a lack of goal-directed behavior which can be associated with abnormalities in dorsolateral prefrontal areas, in caudate dorsal nucleus, and anterior thalamic nuclei (Levy and Dubois, 2006). But it has also been suggested that apathy can arise because of an inability to actually start and execute actions, which is related to the auto-activation subtype as proposed by Levy and Dubois (2006). Kos et al. (2016) suggest that this lack of volunty to move and failure to start motor programs may additionally be due to abnormalities within the inferior parietal cortex (Aarsland et al., 1999; Tekin and Cummings, 2002).

More studies should be directed toward goal specific problems;

1. Create an univocal and well accepted anatomical-pathophysiological integrated model of neural circuits involved in apathy (that should be open and should comprise apathy as a general phenomenon, and not apathy into specific pathologies, such as PD or AD)
2. Define the operative neuropsychological instruments to define in a clinical operative context apathy, in a strong predictive test, not strongly based on caregiver' referral, not limited to patient opinions, or simply by clinical observation
3. Dedicate purposed study to detect the strength of this instrument with the integrative support of modern neuroimaging techniques.

AUTHOR CONTRIBUTIONS

RM and RS design and wrote the manuscript, analyzed the literature, and participated to the final writing and critically drafted the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fnagi.2016.00289/full#supplementary-material

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Sleep Disturbances among Older Adults in the United States, 2002–2012: Nationwide Inpatient Rates, Predictors, and Outcomes

Alyssa A. Gamaldo[1,2,3†], May A. Beydoun[2†], Hind A. Beydoun[4], Hailun Liang[5], Rachel E. Salas[6], Alan B. Zonderman[2], Charlene E. Gamaldo[6‡] and Shaker M. Eid[4‡]*

[1] School of Aging Studies, University of South Florida, Tampa, FL, USA, [2] Behavioral Epidemiology Section, Laboratory of Epidemiology and Population Sciences, National Institute on Aging, NIA/NIH/IRP, Baltimore, MD, USA, [3] Human Development and Family Studies, Penn State University, State College, PA, USA, [4] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [5] Department of Health Policy and Management, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA, [6] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Objective/Background: We examined the rates, predictors, and outcomes [mortality risk (MR), length of stay (LOS), and total charges (TC)] of sleep disturbances in older hospitalized patients.

Patients/Methods: Using the U.S. Nationwide Inpatient Sample database (2002–2012), older patients (≥60 years) were selected and rates of insomnia, obstructive sleep apnea (OSA) and other sleep disturbances (OSD) were estimated using ICD-9CM. TC, adjusted for inflation, was of primary interest, while MR and LOS were secondary outcomes. Multivariable regression analyses were conducted.

Results: Of 35,258,031 older adults, 263,865 (0.75%) had insomnia, 750,851 (2.13%) OSA and 21,814 (0.06%) OSD. Insomnia rates increased significantly (0.27% in 2002 to 1.29 in 2012, *P*-trend < 0.001), with a similar trend observed for OSA (1.47 in 2006 to 5.01 in 2012, *P*-trend < 0.001). TC (2012 $) for insomnia-related hospital admission increased over time from $22,250 in 2002 to $31,527 in 2012, and increased similarly for OSA and OSD; while LOS and MR both decreased. Women with any sleep disturbance had lower MR and TC than men, while Whites had consistently higher odds of insomnia, OSA, and OSD than older Blacks and Hispanics. Co-morbidities such as depression, cardiovascular risk factors, and neurological disorders steadily increased over time in patients with sleep disturbances.

Conclusion: TC increased over time in patients with sleep disturbances while LOS and MR decreased. Further, research should focus on identifying the mechanisms that explain the association between increasing sleep disturbance rates and expenditures within hospital settings and the potential hospital expenditures of unrecognized sleep disturbances in the elderly.

Keywords: sleep disturbances, sleep disorders, inpatient sample, co-morbidity, length of stay, health care cost, mortality, older adults

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***Correspondence:**
May A. Beydoun
baydounm@mail.nih.gov

† Co-first authors.
‡ Co-senior authors.

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INTRODUCTION

Around half of community-dwelling older adults report sleep concerns (Neikrug and Ancoli-Israel, 2010), with overt sleep disorders frequently observed in this population (Wolkove et al., 2007; Neikrug and Ancoli-Israel, 2010; Roepke and Ancoli-Israel, 2010). Specifically, insomnia and obstructive sleep apnea (OSA) are two common disorders affecting Americans 60 years and older (Wolkove et al., 2007; Neikrug and Ancoli-Israel, 2010). The hospital, an under-studied setting, is pertinent since undetected or poorly treated sleep disturbances may account for poor prognosis and long-term utilization of hospital services, thereby increasing healthcare expenditures. As such, this study assesses trends of diagnosed sleep disturbances among older adults within the hospital setting and tests test whether these diagnoses rates are associated with hospitalization metrics (e.g., length of stay, mortality risk, and expenditures).

Sleep disturbances are typically comorbid with medical conditions (Gamaldo et al., 2012b), with the latter presenting obvious and unmanageable symptoms driving older adults to seek treatment in these settings. Those co-morbidities include heart disease (Budhiraja et al., 2011), hypertension (Budhiraja et al., 2011), diabetes (Gottlieb et al., 2005), stroke (Olafiranye et al., 2013), immune system dysfunction (Gamaldo et al., 2012b), stomach ulcers (Budhiraja et al., 2011), arthritis (Budhiraja et al., 2011), migraine (Budhiraja et al., 2011), asthma (Budhiraja et al., 2011), chronic obstructive pulmonary disease(COPD; Budhiraja et al., 2011), neurological complaints(Wolkove et al., 2007; Budhiraja et al., 2011), endocrine dysfunction (Budhiraja et al., 2011), depression and anxiety (Benca, 2014; Jaramillo et al., 2015). Severe levels of co-morbidity both threaten optimal patient care and constitute a public health and safety concern. Chronic untreated sleep disturbances are also linked to impaired cognitive functioning (Gamaldo et al., 2010, 2012a; Zimmerman and Aloia, 2012; Ford et al., 2015), increased traffic accidents (Terán-Santos et al., 1999; Budhiraja et al., 2011), worse quality of life (Daley et al., 2009; Ford et al., 2015), increased risk for disability (Daley et al., 2009; Ford et al., 2015), worse workplace productivity (Leger et al., 2012; Ford et al., 2015), and increased mortality (Hublin et al., 2011; Ford et al., 2015), exerting significant economic strain on the healthcare system (Peppard et al., 2013; Shear et al., 2014; Ford et al., 2015).

With population aging, healthcare service consumption will continuously increase amongst this demographic group at risk for developing and/or exacerbating ailments (Kaufmann et al., 2013). Evaluated as common in samples of community-dwelling older adults (Foley et al., 1995), sleep disturbances' rates remain largely unknown among older adult hospital inpatients. Exploring the hospital setting may support the need for healthcare providers to effectively recognize and treat sleep disturbances among older adults, especially if estimated sleep disturbance rates are lower than previously reported, suggesting under-reporting. Despite prior focus on the impact of sleep disturbances on older adults' physical and/or mental health (Wolkove et al., 2007; Gamaldo et al., 2010; Neikrug and Ancoli-Israel, 2010; Roepke and Ancoli-Israel, 2010), fewer studies examined the ramifications of older adults' sleep disturbances on their interface with the healthcare system particularly as it pertains to inpatient hospital stays. Limited research is available to understand sleep disturbance rates among older adults, examine trends over time, and assess whether co-morbidities and other individual-level and hospital-level characteristics are related to a sleep disturbance diagnosis (i.e., insomnia, OSA, or other sleep disturbance) and hospitalization outcomes.

The current study investigated five key objectives: **(A)** To assess over time trends in the rates of insomnia, OSA, and other sleep disturbances (OSD) among hospitalized older adults; **(B)** To compare patients with and without each of the three classes of sleep disturbance, in terms of co-morbidities, patient-level, and hospital-level characteristics in a recent period of time; **(C)** To compare hospitalization outcomes in patients with and without each of the three classes of sleep disturbance, mortality risk (MR), length of stay (LOS), and total charges (TC) in a recent period of time; **(D)** To examine trends in co-morbidity rates and outcomes of hospitalization among patients with each of the three classes of sleep disturbance; **(E)** To assess the predictive value of patient-level and hospital-level characteristics on outcomes of hospitalization among recently admitted patients with any of the three classes of sleep disturbance.

MATERIALS AND METHODS

Database and Study Participants

The Nationwide Inpatient Sample (NIS) is one of several databases and software tools implemented by the Healthcare Cost and Utilization Project (HCUP)[1], a federal-state-industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ). To date, the NIS is the largest all-payer hospital inpatient care database in the United States. Each year, NIS collects data on nearly 7–8 million hospital stays, reflecting discharges from ∼1000 hospitals, a probability sample from HCUP State Inpatient Databases (SID). The sampling probability is ∼20% and the design is stratified covering U.S. non-rehabilitation, community hospitals, with all acute care hospital discharges in the United States as the target universe. The NIS was developed to provide information on hospital utilization, charges, and quality of care in the United States

NIS defined its sampling strata using five hospital characteristics contained in the AHA hospital files: **(1)** Geographic Region—Northeast, Midwest, West, and South; **(2)** Control—public, private not-for-profit, and proprietary; **(3)** Location—urban or rural; **(4)** Teaching Status—teaching or non-teaching, **(5)** Bed Size—small, medium, and large.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; AIDS, Acquired Immune Deficiency Syndrome; CHF, Congestive Heart Failure; CI, Confidence Interval; HCUP, Healthcare Cost and Utilization Project; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LOS, length of stay; MR, Mortality risk; NIS, Nationwide Inpatient Sample; OR, Odds Ratio; OSA, Obstructive Sleep Apnea; OSD, Other sleep disturbances; SE, Standard Error; SID, State Inpatient Databases; TC, total charges.

[1]Healthcare Cost and Utilization Project (HCUP), Nationwide Inpatient Sample (NIS) Documentation. Available online at: http://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp (Accessed February 5, 2015).

The NIS includes clinical and resource-use information contained within a typical discharge abstract, protecting privacy of patients, physicians, and hospitals. Although NIS data are available since 1988, severity and comorbidity measures contained in the *severity* file became available from 2002 onwards. In addition, NIS did not add new states to its 35-state geographical coverage since 2002 providing more homogeneity in data acquisition over time. Therefore, we used NIS data from 2002 to 2012. Despite the redesign made in 2012, examining trends in means and proportions over the years is possible by inclusion of trend weights, allowing for comparable estimates for all years. (See Appendix I for more details).

Diagnostic Criteria

Each year, the *core* file of NIS provided the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for diagnosis and procedure, from discharge abstract, with information recoded retrospectively. The latest changes to ICD-9-CM codes are provided for 2011: http://www.cdc.gov/nchs/data/icd/ICD-9-CM%20TABULARADDENDAfy12.pdf. The number of diagnoses provided per patient varied by State. However, the number was truncated at 15 for both diagnoses and procedures because few cases had more than 15 diagnoses or procedures between 2002 and 2008. Nevertheless, two variables were provided indicating the total number of diagnoses and procedures. Between 2009 and 2012, up to 25 diagnoses were provided. However, for equal opportunity for a specific diagnosis, only the first 15 were considered for any year.

Among the possible 15 diagnoses, the first ranked diagnosis is termed "principal diagnosis." In our main analysis, trends, characteristics, and outcomes of sleep disturbance as "any diagnosis" of 15 was of primary interest. ICD-9-CM codes used for each class of sleep disturbance as determined by clinical sleep specialist are outline in Appendix II.

Co-morbidity Measure

The AHRQ comorbidity measures identify coexisting medical conditions not directly related to principal diagnosis or main reason for admission, and are likely to have originated before hospital stay. The AHRQ comorbidity measures were developed as one of the HCUP tools. Complete documentation on the comorbidity measures is available on the HCUP User Support Website under Tools & Software. (http://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp). In the present study, all 29 co-morbidities (http://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/Table2-FY12-V3_7.pdf) were included in our analyses. In particular, we examined the likelihood of specific co-morbid conditions among patients with conditions of "insomnia," "OSA," and "OSD" and how this likelihood changed over the years.

Outcome Measures

Three outcome measures of hospitalization were considered, MR upon discharge (0, discharged alive; 1, discharged dead), LOS (days) and TC ($). In particular, we were interested in comparing outcomes in patients with and without a particular "sleep disturbance" in 2012 and examining changes over time among patients with a sleep disturbance between the years of 2002 and 2012. For TC trends, values were inflated to 2012 dollars using the consumer price index.

Covariates

Patient-Level Characteristics

Among patient-level characteristics, we included age (continuous and categorized as 60–64, 65–69, 70–74, 75–79, 80–84, and 85+), sex, race (White, Black, Hispanic, Asian/Pacific Islander, Native American, and Other), median household income for zip code of patient (expressed as quartiles), insurance status (Medicare, Medicaid, Private insurance, self-pay, no charge and other) and admission day (weekday vs. weekend).

Hospital-Level Characteristics

We examined hospital-level characteristics in relation to "sleep disturbance" status and outcomes of healthcare utilization, which included bed size (Small, Medium, Large), ownership of hospital (Government/nonfederal, private non-profit, private investor-owned), location/teaching status of the hospital (rural, urban, non-teaching, urban teaching) and region of the hospital (Northeast, Midwest, South and West).

Statistical Analysis

We used Stata 13.0 (StataCorp, College Station, TX), (STATA, 2013) to analyze data while accounting for survey design complexity based on guidelines outlined by HCUP NIS through incorporation of sampling weights, primary sampling units and strata. Population estimates of proportions, means, and regression coefficients were made (*svy* commands; Stata, 2013). Standard errors were estimated using Taylor series linearization, taking into account sampling weights, strata (combination of five hospital characteristics) and primary sampling units (hospital ID). Multiple regression modeling was also conducted, mainly using linear and logistic regression models, while accounting for sampling design complexity. When waves were combined to examine trends of sleep disturbance rates and outcomes of hospitalization, trend weights were used to ensure redesigned 2012 NIS could be incorporated into the analysis of trends. In order to facilitate analysis of trends using multiple years of NIS data, AHRQ developed new discharge trend weights for the 1993–2011 NIS. These weights were calculated in the same way as the weights for the redesigned 2012 NIS, and were designed for use instead of the original NIS discharge weights for trends analysis. Given that our present trend analysis spans through 2012, starting from 2002, trend weights were used before 2012 data to make estimates comparable to the new 2012 NIS design.

Following our key objectives: **(A)** We first explored proportions of adults 60 years or older who were diagnosed with "insomnia," "OSA," or "OSD" as any of 15 possible recorded diagnoses upon discharge. This analysis was conducted from 2002 to 2012, stratifying by sex and age groups. Overall, within each sex and sex-age groups, we assessed trends by conducting logistic regression analyses with year as the only covariate and "sleep disturbance status" status the binary outcome. **(B)** Sleep disturbance status (yes vs. no) among patients for the year

2012—the most recent available year in NIS—were compared by logistic regression with various predictors of sleep disturbance, including patient-level and hospital-level characteristics as well as patient co-morbidities; **(C)** Using 2012 wave of data among older adults aged 60 years or older, we also compared outcomes of hospitalizations for sleep disturbance and non-sleep disturbance patients by logistic and linear regression models with insomnia, OSA, and OSD status as the main predictor of those outcomes, controlling for patient-level, and hospital-level characteristics, and co-morbidities; **(D)** Using data from 2002 through 2012, we conducted a trends analysis of co-morbidities among patients with each of the three classes of sleep disturbance, by estimating proportions with their *SE* and conducting a logistic regression model for each comorbidity with year being the only predictor. Similarly, we examined trends in MR, LOS, and TC using the same methods (i.e., proportion estimation and multiple regression models with year as the only covariates) among patients with each class of sleep disturbance. Another linear model was also conducted to examine the net trend in those three parameters after adjustment for age, sex, and total number of co-morbidity; **(E)** Finally, and using analyses similar to **(C)** but restricting the sample to patients with any sleep disturbance, we ran several regression models testing predictors of hospitalization outcomes in 2012 among older adults, while including insomnia, OSA and OSD status as additional covariates in the model. The secondary analysis of NIS was approved by the institutional review boards of the NIH and Johns Hopkins School of Medicine.

RESULTS

Of 87,039,711 patients sampled from 2002 to 2012, NIS (weighted mean age ± *SE*: 47.9 ± 0.2, and weighted proportion female ± *SE*: 58.5% ± 0.1, weighted number of discharges: 411,487,801), 35,258,031 were aged 60 years or older (weighted mean age ± SE: 75.37 ± 0.03, and weighted proportion female ± *SE*: 56.0% ± 0.1). The total weighted number of hospital discharges of older adults aged 60 years or older between 2002 and 2012 was estimated at 166,871,086 nationwide. In 2012, the unweighted number of discharges over 60 years of age was 2,825,130; the weighted number was 14,126,650.

Of the 35,258,031 older adults in the unweighted sample (2002–2012), 263,865 had insomnia as "any diagnosis" (weighted percent of discharges ± *SE*: 0.75 ± 0.01); 750,851 had an OSA diagnosis (weighted percent of discharges ± *SE*: 2.14 ± 0.04), 21,814 had a diagnosis of OSD (weighted percent of discharges ± *SE*: 0.06 ± 0.00).

Table S1 and **Figure 1** shows the trends in weighted proportions of all three classes of sleep disturbance as any diagnosis, stratifying by sex (**Objective A**). Overall and among men and women, there was an increasing trend in the share of hospitalizations of older adults who were diagnosed with insomnia, OSA, and OSD. A linear trend was particularly observed for insomnia diagnosis, with an estimated rate of 0.27% overall in 2002 rising linearly up to 1.29% in 2012. In contrast, OSA was not diagnosed until 2005 in this inpatient sample (estimated rate of 0.21%) and its rate rose sharply thereafter to reach a level of 5% out of all hospitalizations in 2012. Men

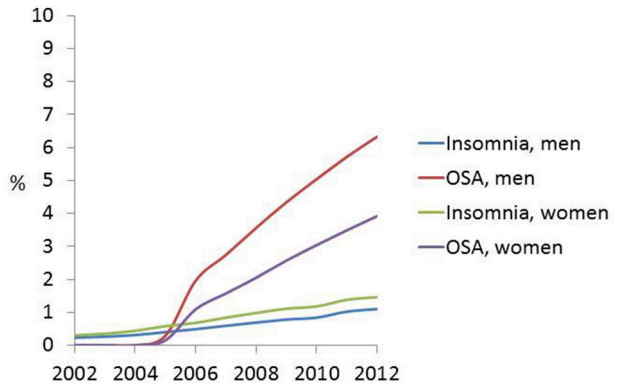

FIGURE 1 | Sex-specific and overall time trends in insomnia, obstructive sleep apnea. (OSA) and other sleep disturbances (OSD) (as any diagnosis) rates in the inpatient older adult population (60+y); NIS, 2002–2012.

tended to have higher rates of OSA compared to women in all years, while the reverse gender difference was true for insomnia (Table S1). Stratifying by both sex and age group, Table S2 and **Figures 2A–F** shows that in later years (particularly beyond 2009), the young-old (60–64 years) tended to have higher rates of insomnia and OSA compared to older groups and specifically the oldest-old (85+).

Table 1 shows the association of patient and hospital-level characteristics with all three classes of sleep disturbance status among hospitalized older adults (**Objective B**). In general, insomnia status was positively associated with being female, belonging to a younger age group, a White ethnicity, higher income, having Medicare as the primary expected insurance, admission on a weekday, admission to a small bed size (vs. large bed size) or private, investor-owned hospital as opposed to government, and with rural hospitalizations. Geographically speaking, the Northeast had the lowest likelihood of insomnia diagnosis whereas the West had the highest rates. Several co-morbidities were more prevalent in non-insomnia cases compared to insomnia, while others showed no difference. The few exceptions whereby having a co-morbidity was independently linked to higher odds of insomnia included alcohol abuse (OR = 1.17, 95% CI:1.10–1.25, $p < 0.001$), anemia (OR = 1.07, 95% CI:1.04–1.11, $p < 0.001$), depression (OR = 2.73, 95%CI: 2.66–2.81, $p < 0.001$), drug abuse (OR = 1.56, 95%CI:1.44–1.70, $p < 0.001$), hypertension (OR = 1.09, 95%CI:1.06–1.12), hypothyroidism (OR = 1.08, 95%CI: 1.05–1.11, $p < 0.001$), neurological disorders (OR = 1.17, 95%CI:1.13–1.21) and psychoses (OR = 1.98, 95%CI:1.89–2.08, $p < 0.001$).

In contrast, the odds of an OSA diagnoses was greater among men, but lower with age, significantly higher among Whites and patients with higher income, and generally higher among Medicare beneficiaries. The odds for diagnosis with OSA was lower in weekend admissions as was insomnia, but the odds was higher with bed size, highest in private non-profit and urban hospitals, while remaining lowest in the Northeast. Several co-morbidities had independent positive

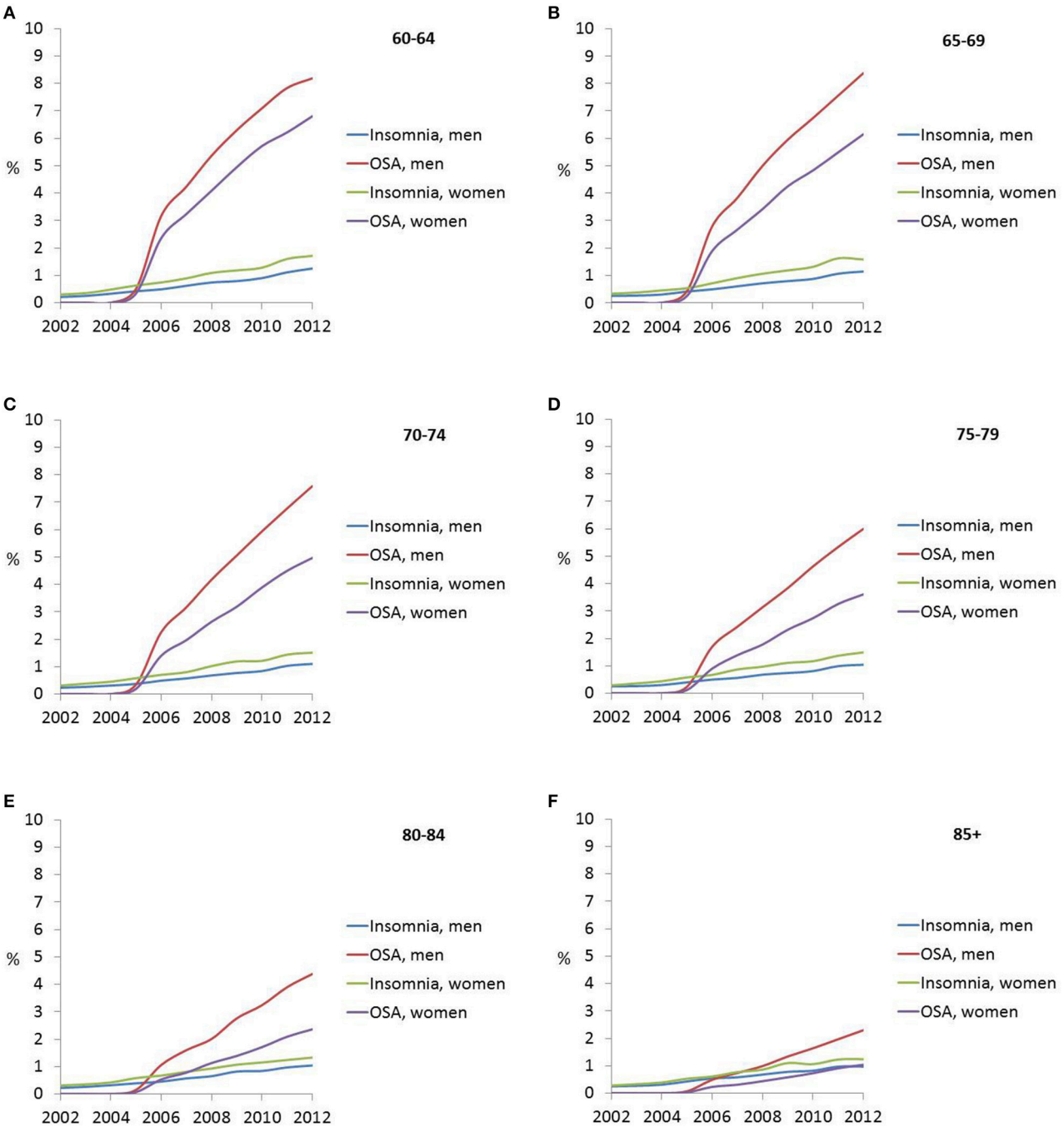

FIGURE 2 | (A–F) Sex- and age-specific time trends in insomnia, obstructive sleep apnea. (OSA) and other sleep disturbances (OSD) (as any diagnosis) rates in the inpatient older adult population (60+y); NIS, 2002–2012.

associations with OSA and many of those intersected with those observed with insomnia. These included rheumatoid arthritis, congestive heart failure, depression, diabetes (both uncomplicated and complicated), hypertension, hypothyroidism, neurological disorders, pulmonary circulation disorders, renal failure, and most importantly obesity (OR = 5.15, 95%CI: 5.05–5.25, $p < 0.001$).

The likelihood of OSD diagnoses was not modified by gender or income though was still lowest among the oldest-old, and highest among Whites. Hospital-level characteristics were associated with OSD in a way similar to that of OSA, with the odds doubled in the Midwest compared to the Northeast. Most notably, while alcohol abuse was inversely related to OSD, drug abuse was among the strongest predictors of OSD (OR = 8.52,

TABLE 1 | Associations of patient and hospital characteristics with insomnia, OSA, and OSD (1, Yes; 0, No) among the US inpatient older adult population: multiple logistic regression models (Unweighted *N* = 2,825,283; Weighted *N* = 14,126,415)*, NIS 2012.

	Unwt. N*	Wt. % ± *SE**	Insomnia			OSA			OSD		
		60 + y, 2012	OR**	95% CI	*P*	OR**	95% CI	*P*	OR**	95% CI	*P*
Female	1,677,164	55.1 ± 0.1	1.19	(1.16;1.22)	< 0.001	0.53	(0.52;0.54)	< 0.001	0.98	(0.90;1.07)	0.71
AGE GROUP											
60–64	503,657	16.5 ± 0.1	1			1			1		
65–69	531,122	17.4 ± 0.1	0.91	(0.88;0.95)	< 0.001	0.89	(0.87;0.91)	< 0.001	0.95	(0.83;1.10)	0.53
70–74	490,322	16.1 ± 0.0	0.90	(0.86;0.94)	< 0.001	0.78	(0.77;0.80)	< 0.001	1.02	(0.87;1.19)	0.83
74–79	470,935	15.5 ± 0.0	0.89	(0.85;0.93)	< 0.001	0.64	(0.62;0.65)	< 0.001	0.90	(0.76;1.06)	0.21
80–84	452,445	14.9 ± 0.0	0.84	(0.80;0.88)	< 0.001	0.48	(0.46;0.49)	< 0.001	0.82	(0.69;0.98)	0.027
85+	597,194	19.6 ± 0.0	0.76	(0.73;0.80)	< 0.001	0.26	(0.25;0.27)	< 0.001	0.72	(0.61;0.86)	< 0.001
RACE											
1 = White	2,232,525	77.3 ± 0.4	1			1			1		
2 = Black	312,331	10.8 ± 0.0	0.62	(0.59;0.66)	< 0.001	0.88	(0.85;0.92)	< 0.001	0.66	(0.56;0.79)	< 0.001
3 = Hispanic	194,468	6.7 ± 0.0	0.87	(0.81;0.94)	< 0.001	0.63	(0.60;0.67)	< 0.001	0.67	(0.53;0.87)	0.002
4 = Asian/Pacific Islander	58,023	2.0 ± 0.0	0.87	(0.78;0.97)	0.014	0.47	(0.43;0.52)	< 0.001	0.67	(0.44;1.01)	0.05
5 = Native American	15,399	0.5 ± 0.1	0.84	(0.70;1.00)	0.05	0.93	(0.78;1.11)	0.44	0.31	(0.13;0.75)	0.009
6 = Other	76,738	2.7 ± 0.2	0.96	(0.87;1.06)	0.47	0.72	(0.67;0.79)	< 0.001	1.03	(0.80;1.32)	0.81
MEDIAN HH INCOME FOR ZIP CODE OF PATIENT											
1st quartile	873,930	29.3 ± 0.5	1			1			1		
2nd quartile	754,442	25.3 ± 0.4	1.01	(0.97;1.05)	0.62	1.09	(1.06;1.12)	< 0.001	0.97	(0.85;1.10)	0.65
3rd quartile	710,554	23.8 ± 0.3	1.04	(1.00;1.09)	0.08	1.16	(1.13;1.20)	< 0.001	0.95	(0.82;1.09)	0.47
4th quartile	646,730	21.7 ± 0.5	1.08	(1.02;1.14)	0.008	1.20	(1.15;1.24)	< 0.001	1.08	(0.93;1.25)	0.33
INSURANCE STATUS											
Medicare	2,432,075	80.0 ± 0.2	1			1			1		
Medicaid	100,551	3.3 ± 0.1	0.90	(0.83;0.96)	0.003	0.69	(0.66;0.73)	< 0.001	0.68	(0.52;0.91)	0.008
Private insurance	409,617	13.4 ± 0.2	0.97	(0.93;1.02)	0.25	1.01	(0.98;1.03)	0.49	1.10	(0.96;1.26)	0.16
Self-pay	39,753	1.3 ± 0.0	0.71	(0.61;0.82)	< 0.001	0.49	(0.45;0.54)	< 0.001	0.91	(0.60;1.39)	0.67
No charge	3441	0.1 ± 0.0	1.03	(0.73;1.46)	0.87	0.56	(0.41;0.76)	< 0.001	1.08	(0.34;3.41)	0.89
Other	54,012	1.8 ± 0.1	0.86	(0.78;0.95)	0.003	0.86	(0.81;0.90)	< 0.001	0.84	(0.60;1.17)	0.29
ADMISSION DAY											
Weekday	2,440,195	80.1 ± 0.0	1			1			1		
Weekend	605,477	19.9 ± 0.1	0.95	(0.93;0.98)	0.001	0.94	(0.92;0.95)	< 0.001	0.91	(0.81;1.01)	0.08
CO-MORBIDITY											
AIDS	2002	0.1 ± 0.0	0.61	(0.34;1.10)	0.10	0.47	(0.34;0.65)	< 0.001	0.70	(0.10;5.02)	0.72
Alcohol Abuse	80,337	2.6 ± 0.0	1.17	(1.10;1.25)	< 0.001	0.59	(0.56;0.61)	< 0.001	0.72	(0.55;0.95)	0.018
Deficiency Anemia	670,473	22.0 ± 0.1	1.07	(1.04;1.11)	< 0.001	0.92	(0.91;0.94)	< 0.001	0.97	(0.86;1.09)	0.57
Rheumatoid arthritis/collagen vascular disease	108,420	3.6 ± 0.0	1.01	(0.95;1.06)	0.82	1.18	(1.15;1.22)	< 0.001	1.14	(0.93;1.39)	0.20
Chronic blood loss anemia	39,495	1.3 ± 0.0	0.98	(0.87;1.10)	0.71	0.79	(0.74;0.84)	< 0.001	1.01	(0.68;1.50)	0.96
Congestive heart failure	420,652	13.8 ± 0.1	0.77	(0.74;0.80)	< 0.001	1.37	(1.34;1.39)	< 0.001	0.80	(0.69;0.92)	0.002
Chronic pulmonary disease	720,894	23.7 ± 0.1	0.97	(0.94;0.99)	< 0.001	1.79	(1.76;1.81)	< 0.001	1.02	(0.93;1.13)	0.63
Coagulopathy	176,187	5.8 ± 0.0	0.80	(0.76;0.85)	< 0.001	0.88	(0.86;0.91)	< 0.001	0.61	(0.47;0.78)	< 0.001
Depression	356,534	11.7 ± 0.1	2.73	(2.66;2.81)	< 0.001	1.37	(1.35;1.43)	< 0.001	1.99	(1.80;2.21)	< 0.001
Diabetes, uncomplicated	802,141	26.3 ± 0.1	0.73	(0.71;0.76)	< 0.001	1.50	(1.48;1.52)	< 0.001	0.84	(0.76;0.93)	0.001
Diabetes, complicated	179,761	5.9 ± 0.1	0.69	(0.65;0.73)	< 0.001	1.39	(1.35;1.43)	< 0.001	0.79	(0.64;0.98)	0.036
Drug abuse	29,617	0.1 ± 0.0	1.56	(1.44;1.70)	< 0.001	0.72	(0.68;0.77)	< 0.001	8.52	(7.02;10.34)	< 0.001
Hypertension	2,109,734	69.3 ± 0.1	1.09	(1.06;1.12)	< 0.001	1.21	(1.20;1.23)	< 0.001	1.02	(0.93;1.12)	0.62
Hypothyroidism	512,730	16.8 ± 0.1	1.08	(1.05;1.11)	< 0.001	1.22	(1.20;1.24)	< 0.001	1.15	(1.03;1.28)	0.013
Liver disease	72,826	2.4 ± 0.0	0.91	(0.84;0.97)	0.009	0.86	(0.83;0.90)	< 0.001	0.86	(0.63;1.17)	0.34

(Continued)

TABLE 1 | Continued

	Unwt. N*	Wt. % ± *SE**	Insomnia			OSA			OSD		
		60 + y, 2012	OR**	95% CI	*P*	OR**	95% CI	*P*	OR**	95% CI	*P*
Lymphoma	34,835	1.1 ± 0.0	0.94	(0.84;1.04)	0.23	0.84	(0.79;0.90)	< 0.001	0.81	(0.51;1.28)	0.38
Fluid/electrolyte disorders	897,369	29.5 ± 0.1	0.92	(0.90;0.95)	< 0.001	0.82	(081;0.83)	< 0.001	0.83	(0.75;0.92)	0.001
Metastatic cancer	90,230	3.0 ± 0.0	0.83	(0.77;0.89)	< 0.001	0.52	(0.50;0.55)	< 0.001	0.61	(0.44;0.84)	0.003
Neurological disorders	301,899	9.9 ± 0.0	1.17	(1.13;1.21)	< 0.001	1.13	(1.10;1.15)	< 0.001	1.52	(1.35;1.71)	< 0.001
Obesity	329,904	10.8 ± 0.1	0.90	(0.86;0.93)	< 0.001	5.15	(5.05;5.25)	< 0.001	1.36	(1.20;1.54)	< 0.001
Paralysis	88,068	2.9 ± 0.0	0.93	(0.86;1.00)	0.042	0.68	(0.65;0.71)	< 0.001	1.18	(0.91;1.54)	0.20
Peripheral vascular disorders	292,442	9.6 ± 0.0	0.80	(0.76;0.83)	< 0.001	0.83	(0.81;0.85)	< 0.001	0.85	(0.72;1.01)	0.07
Psychoses	111,610	3.7 ± 0.0	1.98	(1.89;2.08)	< 0.001	0.95	(0.91;0.98)	0.003	1.75	(1.47;2.10)	< 0.001
Pulmonary circulation disorders	97,609	3.2 ± 0.0	0.79	(0.76;0.83)	< 0.001	1.70	(1.65;1.75)	< 0.001	0.98	(0.75;1.28)	0.90
Renal failure	562,107	18.5 ± 0.1	0.73	(0.71;0.76)	< 0.001	1.14	(1.12;1.17)	< 0.001	0.70	(0.61;0.80)	< 0.001
Non-metastatic cancer	91,610	3.0 ± 0.0	0.97	(0.91;1.03)	0.28	0.72	(0.70;0.75)	< 0.001	0.65	(0.47;0.92)	0.014
Peptic ulcer	1222	0.0 ± 0.0	1.09	(0.67;1.78)	0.72	0.68	(0.48;0.95)	0.025	4.58	(1.72;12.20)	0.002
Valvular disease	176,782	5.8 ± 0.1	0.98	(0.93;1.04)	0.53	0.99	(0.96;1.02)	0.40	1.14	(0.94;1.39)	0.18
Weight loss	193,961	6.4 ± 0.1	0.84	(0.80;0.89)	< 0.001	0.45	(0.44;0.47)	< 0.001	0.90	(0.74;1.09)	0.29
BED SIZE											
Small	458,999	15.0 ± 0.0	1			1			1		
Medium	801,171	26.3 ± 0.0	0.95	(0.89;1.02)	0.17	1.06	(1.00;1.12)	0.048	0.96	(0.80;1.16)	0.70
Large	1,785,505	58.6 ± 0.0	0.92	(0.87;0.98)	0.010	1.11	(1.05;1.17)	< 0.001	0.80	(0.67;0.95)	0.009
OWNERSHIP OF HOSPITAL											
Government, nonfederal	321,524	10.6 ± 0.0	1			1			1		
Private, non-profit	2,275,706	74.7 ± 0.0	1.02	(0.94;1.10)	0.71	1.12	(1.04;1.20)	0.003	1.26	(1.04;1.53)	0.019
Private, investor-own	448,445	14.7 ± 0.0	1.11	(1.01;1.22)	0.033	0.98	(0.90;1.07)	0.61	1.10	(0.86;1.40)	0.47
LOCATION/TEACHING STATUS											
Rural	404,639	13.3 ± 0.0	1			1			1		
Urban, non-teaching	1,232,393	40.5 ± 0.0	0.80	(0.74;0.85)	< 0.001	1.23	(1.16;1.32)	< 0.001	0.77	(0.65;0.91)	0.002
Urban, teaching	1,408,643	46.3 ± 0.0	0.82	(0.76;0.88)	< 0.001	1.46	(1.37;1.56)	< 0.001	0.70	(0.59;0.83)	< 0.001
REGION OF HOSPITAL											
Northeast	612,680	20.1 ± 0.4	1			1			1		
Midwest	715,874	23.5 ± 0.4	1.27	(1.17;1.38)	< 0.001	1.36	(1.27;1.45)	< 0.001	2.00	(1.67;2.40)	< 0.001
South	1,175,080	38.6 ± 0.5	1.44	(1.33;1.56)	< 0.001	1.18	(1.11;1.25)	< 0.001	1.75	(1.47;2.07)	< 0.001
West	542,041	17.8 ± 0.3	1.61	(1.48;1.76)	< 0.001	1.12	(1.04;1.21)	< 0.001	1.58	(1.29;1.93)	< 0.001
Female	1,677,164	55.1 ± 0.1	1.19	(1.16;1.22)	< 0.001	0.53	(0.52;0.54)	< 0.001	0.98	(0.90;1.07)	0.71

NIS, Nationwide Inpatient Sample; OSA, Obstructive Sleep Apnea; OSD, Other Sleep Disturbances; Unwt, Unweighted; Wt, Weighted.

**Sample sizes and % were based on data availability per covariate among older adults 60 + y in the NIS 2012. Unweighted and weighted N are based on simultaneous availability of data in the logistic regression models.*

***Odds ratios (OR) are estimated from a multiple logistic regression model with their 95% confidence interval (CI) and thus are multivariate-adjusted for all covariates included in the model. OR are interpreted as the odds of having the outcome of interest among the exposed group(s) relative to the odds of having the outcome of interest among the unexposed group (referent category), controlling for all other covariates in the model.*

95%CI:7.02–10.34, $p < 0.001$) followed by peptic ulcer (OR = 4.58, 95%CI:1.72–12.20, $p = 0.002$). Other co-morbidities that were positively linked to OSD included depression, hypertension, neurological disorders, obesity, and psychoses.

Table 2 displays findings from multiple regression models testing associations between the three classes of sleep disturbance as predictors of MR, LOS, and TC, while adjusting for individual-level and hospital-level characteristics (**Objective C**). Generally, diagnosis with any of the three sleep disturbances was associated with lower MR and lower TC compared to non-diagnosis. LOS was higher for insomnia vs. non-insomnia and for OSD vs. non-OSD, though the reverse pattern was observed for OSA status.

Among hospitalized older adults who were diagnosed with each of the three classes of sleep disturbances, trends in co-morbidities from 2002 to 2012 are presented in Table S3 (**Objective D**). Overall, the average number of co-morbidities increased steadily from 2.28 in 2002 to 3.10 in 2012 for insomnia, from 3.11(2005) to 3.87(2012) for OSA and 1.92(2002) to 3.19(2012) for OSD. Some of the most prevalent co-morbidities

TABLE 2 | Outcomes of healthcare utilization (MR, LOS, and TC) among older adults by sleep disturbance status, patient-level, and hospital-level characteristics: multiple logistic and OLS regression models, NIS 2012.

	Model 1: MR			Model 2: LOS (days)			Model 3: TC ($)		
	OR**	95% CI	*P*	β**	(SE)	*P*	β**	(SE)	*P*
INSOMNIA STATUS									
Non-insomnia	1			–			–		
Insomnia (any diagnosis)	0.36	(0.32;0.40)	<0.001	+0.44	(0.05)	<0.001	–4715	(339)	<0.001
OSA STATUS									
Non-OSA	1			–			–		
OSA (any diagnosis)	0.58	(0.56;0.61)	<0.001	–0.34	(0.02)	<0.001	–2125	(316)	<0.001
OSD STATUS									
Non-OSD	1			–			–		
OSD (any diagnosis)	0.35	(0.23;0.54)	<0.001	+0.40	(0.12)	0.001	–5853	(787)	<0.001
Unwt. N*		2,824,671			2,825,124		2,767,001		
Wt. N*		14,123,355			14,125,620		13,835,005		

LOS, Length of stay; MR, mortality Risk; NIS, Nationwide Inpatient Sample; OSA, Obstructive Sleep Apnea; OSD, Other Sleep Disturbances; TC, Total Charges; Unwt, Unweighted; Wt, Weighted.

**Weighted and unweighted sample sizes are based on multiple logistic regression models with outcome being "all sleep disturbances."*

***Odds ratios (OR) are estimated from a multiple logistic regression model with their 95% confidence interval (CI) and linear regression coefficients (β) are estimated from multiple ordinary least square (OLS) models with their standard errors (SE) and thus are multivariate-adjusted for all covariates included in the model. OR are interpreted as the odds of mortality among the exposed group(s) relative to the odds of mortality among the unexposed group (referent category), controlling for all other covariates in the model. β is the estimated adjusted difference in LOS or TC between referent and exposure category(ies). All models controlled for sex, age, race, income, insurance status, admission day, co-morbidity, hospital bed size, ownership of hospital, location/teaching status, and region of the hospital.*

(>10% in 2012) in insomnia patients included deficiency anemia (∼14% in 2002 → 21% in 2012), chronic pulmonary disorder (22% in 2002 → 24% in 2012), depression (20% in 2002 → 27% in 2012), uncomplicated diabetes (∼15% in 2002 → 21% in 2012), hypertension (52% in 2002 → 70% in 2012), hypothyroidism (14% in 2002 → 20% in 2012), fluid/electrolyte disorder (18% in 2002 → 27% in 2012), neurological disorders (6.3% in 2002 →12.5% in 2012), and renal failure (3% in 2002 → 12% in 2012). Except for congestive heart failure, the rates among insomnia patients rose over time for most co-morbidities. Among OSA patients, the most prevalent co-morbidities included those observed among insomnia patients in addition to obesity (42% in 2012) and congestive heart failure (19% in 2012). Despite similar comorbidity patterns between the three classes of sleep disturbance, OSD had the highest co-morbidity with drug abuse compared to insomnia and OSA (7.5% in 2012 vs. 1.8 for insomnia and 0.9% in OSA).

In parallel with the rise in co-morbidities among older adult patients with sleep disturbance, TC rose steadily from an average of $22,250/admission in 2002 to $38,177/admission in 2012 for insomnia with similar mean annual changes observed for OSA and OSD ($1414/year for OSA, $1635/year for OSD and $1722/year for insomnia). The rate of increase in cost was slightly attenuated but remained significant after adjustment for age, sex, and total number of co-morbidities. However, both MR and LOS have been markedly reduced over-time, with the exception of MR for OSD ($p > 0.05$). In particular, MR dropped steadily from 1.5% in 2002 to 1.0% in 2012 among insomnia patients while mean LOS was reduced from 6.1 days in 2002 to 5.4 days in 2012. Those rates of decrease over time were even more marked after control was made on age, sex, and total number of co-morbidities (Table S4, **Objective D**).

Using data from 2012 on inpatient older adults with "any sleep disturbance," we tested predictors of outcomes of hospitalization (**Table 3**, **Objective E**). MR was lower among women who also had a significantly lower TC. MR increased linearly with age, with longer LOS but lower TC observed in the older groups. TC was also higher among Hispanics and other ethnic groups compared to Whites, with Blacks having significantly lower MR and higher LOS compared to Whites. The 4th quartile of income was significantly more expensive in terms of TC compared to the 1st quartile, though LOS was shorter and MR lower.

DISCUSSION

This study is the first to utilize a large national healthcare database to comprehensively examine trends in sleep disturbance diagnoses of insomnia, OSA, and OSD among hospitalized older adults in the United States and whether co-morbidities and outcomes are related to disturbance status. Moreover, this study tested both patient-level and hospital-level predictors of sleep disturbance status and outcomes of hospitalization.

Our study observed that the proportion of older adults with a sleep diagnosis has increased significantly over the last decade. Insomnia and OSA diagnoses in older adults have more than tripled from 2002 to 2012, while diagnoses for OSD have almost doubled over this period. A study using the National Health Interview Survey (Ford et al., 2015) observed similar increasing rate trends specifically for insomnia from 2002 (17.5%) and 2012 (19.2%) with adults 18 years and older. The study also observed greater rate changes over time for the youngest-old (55–64 years: 22.1–24.2%) and middle-old (65–74 years: 18.6–21.3%) than the oldest-old (75 years and older: 20.5–20.7%) age groups. The current study expands upon these findings, in that

TABLE 3 | Outcomes of healthcare utilization (MR, LOS, and TC) among older adults with "any sleep disturbance," patient-level and hospital-level characteristics: multiple logistic and OLS regression models, NIS 2012.

			Model 1: MR			Model 2: LOS(days)			Model 3: TC ($)		
	Unwt. N*	Wt. % ± *SE**	OR	95% CI	*P*	β	(SE)	*P*	β	(SE)	*P*
Insomnia (yes vs. no)	39,430	20.5 ± 0.3	0.35	(0.18;0.69)	0.003	+0.09	(0.10)	0.34	−3424	(1143)	0.003
OSA (yes vs. no)	152,299	79.2 ± 0.3	0.56	(0.28;1.12)	0.10	−0.62	(0.11)	< 0.001	+2222	(1126)	0.049
Other disturbance (yes vs. no)	2249	1.3 ± 0.0	0.35	(0.15;0.82)	0.015	+0.07	(0.64)	0.64	−4788	(1259)	< 0.001
Female	90,673	47.2 ± 0.2	0.91	(0.84;1.00)	0.045	−0.04	(0.03)	0.18	−2984	(292)	< 0.001
AGE											
60–64	45,224	23.5 ± 0.1	1			–			–		
65–69	45,694	23.8 ± 0.1	1.29	(1.12;1.51)	0.001	+0.03	(0.04)	0.44	+507	(447)	0.26
70–74	37,005	19.2 ± 0.1	1.64	(1.40;1.93)	< 0.001	+0.10	(0.05)	0.046	−1106	(527)	0.036
74–79	28,279	14.7 ± 0.1	1.82	(1.54;2.14)	< 0.001	+0.18	(0.05)	0.001	−2752	(552)	< 0.001
80–84	20,166	10.5 ± 0.1	2.22	(1.87;2.62)	< 0.001	+0.33	(0.06)	< 0.001	−4413	(607)	< 0.001
85+	15,956	8.3 ± 0.1	3.07	(2.58;3.65)	< 0.001	+0.21	(0.08)	0.011	−9022	(653)	< 0.001
RACE											
1 = White	147,852	81.6 ± 0.4	1			–			–		
2 = Black	18,194	10.0 ± 0.3	0.82	(0.71;0.95)	0.007	+0.15	(0.06)	0.011	+442	(946)	0.64
3 = Hispanic	8542	4.7 ± 0.2	1.00	(0.83;1.20)	0.97	+0.03	(0.09)	0.70	+6356	(1449)	< 0.001
4 = Asian/Pacific Islander	1776	1.0 ± 0.1	1.04	(0.73;1.49)	0.81	+0.29	(0.17)	0.09	+3430	(2743)	0.21
5 = Native American	961	0.5 ± 0.1	1.09	(0.66;1.80)	0.73	−0.01	(0.22)	0.97	−7306	(3649)	0.045
6 = Other	3792	2.1 ± 0.2	0.91	(0.68;1.20)	0.49	+0.23	(0.11)	0.039	+5045	(2487)	0.043
MEDIAN HH INCOME FOR ZIP CODE OF PATIENT											
1st quartile	51,128	27.1 ± 0.5	1			–			–		
2nd quartile	48,773	25.8 ± 0.4	0.95	(0.86;1.06)	0.37	−0.15	(0.04)	< 0.001	−181	(553)	0.74
3rd quartile	48,015	25.4 ± 0.4	0.85	(0.76;0.95)	0.005	−0.19	(0.05)	< 0.001	+1045	(657)	0.11
4th quartile	41,027	21.7 ± 0.6	0.80	(0.70;0.90)	< 0.001	−0.29	(0.05)	< 0.001	+4623	(1001)	< 0.001
INSURANCE STATUS											
Medicare	147,649	76.9 ± 0.2	1			–			–		
Medicaid	5650	2.9 ± 0.7	1.34	(1.04;1.74)	0.026	+0.83	(0.18)	< 0.001	−1050	(956)	0.27
Private insurance	33,410	17.4 ± 0.2	1.17	(1.00;1.35)	0.046	−0.05	(0.04)	0.18	+1622	(556)	0.004
Self-pay	1543	0.8 ± 0.0	1.18	(0.66;1.96)	0.64	+1.06	(0.28)	< 0.001	+3232	(3804)	0.40
No charge	166	0.1 ± 0.1	0.69	(0.09;5.13)	0.72	+1.69	(1.05)	0.11	−6771	(3856)	0.08
Other	3618	1.9 ± 0.1	2.30	(1.77;2.99)	< 0.001	+0.15	(0.11)	0.18	+1076	(1159)	0.35
ADMISSION DAY											
Weekday	157,416	81.8 ± 0.1	1			–			–		–
Weekend	34,908	18.2 ± 0.1	1.41	(1.29;1.54)	< 0.001	−0.12	(0.03)	0.001	−6191	(359)	< 0.001
CO-MORBIDITY											
AIDS	64	0.0 ± 0.0	–	–		−0.13	(0.70)	0.86	+5272	(10,096)	0.60
Alcohol Abuse	4114	2.1 ± 0.0	1.06	(0.80;1.41)	0.66	+0.37	(0.10)	< 0.001	−2616	(1,011)	0.010
Deficiency Anemia	40,039	20.8 ± 0.2	0.94	(0.85;1.03)	0.21	+0.96	(0.04)	< 0.001	+5761	(449)	< 0.001
Rheumatoid arthritis/collagen vascular disease	7661	4.0 ± 0.1	1.02	(0.83;1.26)	0.85	+0.02	(0.06)	0.70	−946	(606)	0.12
Chronic blood loss anemia	2023	1.1 ± 0.0	0.91	(0.64;1.30)	0.62	+1.15	(0.12)	< 0.001	+10,899	(1419)	< 0.001
Congestive heart failure	33,552	17.4 ± 0.1	1.61	(1.47;1.77)	< 0.001	+0.68	(0.04)	< 0.001	−1934	(402)	< 0.001
Chronic pulmonary disease	66,136	34.3 ± 0.2	1.24	(1.14;1.34)	< 0.001	+0.34	(0.03)	< 0.001	+2705	(349)	< 0.001
Coagulopathy	9448	4.9 ± 0.1	1.77	(1.55;2.02)	< 0.001	+1.24	(0.07)	< 0.001	+20,020	(1666)	< 0.001
Depression	35,872	18.7 ± 0.2	0.82	(0.73;0.92)	0.001	−0.06	(0.03)	0.049	−1862	(354)	< 0.001
Diabetes, uncomplicated	68,935	35.8 ± 0.2	1.07	(0.98;1.17)	0.11	+0.07	(0.03)	0.009	−1274	(303)	< 0.001
Diabetes, complicated	16,689	8.7 ± 0.1	0.81	(0.71;0.95)	0.007	+0.55	(0.05)	< 0.001	+118	(657)	0.86

(Continued)

TABLE 3 | Continued

			Model 1: MR			Model 2: LOS(days)			Model 3: TC ($)		
	Unwt. N*	Wt. % ± *SE**	OR	95% CI	*P*	β	(SE)	*P*	β	(SE)	*P*
Drug abuse	2175	1.1 ± 0.0	0.71	(0.43;1.15)	0.16	+0.16	(0.12)	0.16	−1799	(1265)	0.16
Hypertension	143,908	74.8 ± 0.1	0.78	(0.72;0.95)	< 0.001	−0.08	(0.03)	0.005	+2170	(337)	< 0.001
Hypothyroidism	35,425	18.4 ± 0.1	0.86	(0.77;0.95)	0.005	+0.02	(0.03)	0.50	+78	(324)	0.81
Liver disease	4538	2.4 ± 0.0	1.15	(0.90;1.46)	0.26	−0.06	(0.08)	0.47	−4404	(930)	< 0.001
Lymphoma	4528	0.9 ± 0.0	1.89	(1.42;2.52)	< 0.001	+0.72	(0.16)	< 0.001	+259	(1606)	0.87
Fluid/electrolyte disorders	48,524	25.2 ± 0.2	2.29	(2.10;2.50)	< 0.001	+1.26	(0.04)	< 0.001	+8318	(537)	< 0.001
Metastatic cancer	3131	1.6 ± 0.0	3.03	(2.48;2.50)	< 0.001	+0.91	(0.12)	< 0.001	+3130	(1265)	0.013
Neurological disorders	19,151	10.0 ± 0.1	1.24	(1.10;1.40)	0.001	+0.38	(0.05)	< 0.001	−539	(537)	0.32
Obesity	67,602	35.2 ± 0.2	1.00	(0.91;1.09)	0.97	+0.48	(0.03)	< 0.001	+4033	(357)	< 0.001
Paralysis	4230	2.2 ± 0.0	1.31	(1.03;1.67)	0.025	+3.56	(0.17)	< 0.001	+11,422	(1620)	< 0.001
Peripheral vascular disorders	17,437	9.1 ± 0.1	1.06	(0.94;1.21)	0.33	+0.06	(0.04)	0.12	+3507	(499)	< 0.001
Psychoses	8623	4.5 ± 0.1	0.86	(0.70;1.07)	0.18	+0.58	(0.08)	< 0.001	−1471	(716)	0.040
Pulmonary circulation disorders	10,263	5.3 ± 0.1	1.85	(1.63;2.09)	< 0.001	+0.88	(0.06)	< 0.001	+4340	(776)	< 0.001
Renal failure	40,066	20.8 ± 0.2	1.58	(1.44;1.73)	< 0.001	+0.13	(0.04)	< 0.001	−1839	(423)	< 0.001
Non-metastatic cancer	4289	2.2 ± 0.0	1.79	(1.46;2.18)	< 0.001	+0.40	(0.09)	< 0.001	−2250	(841)	0.007
Peptic ulcer	60	0.0 ± 0.0	–	–		−0.10	(0.58)	0.86	−1823	(5881)	0.22
Valvular disease	10,923	5.7 ± 0.1	1.01	(0.87;1.16)	0.93	+0.06	(0.05)	0.26	−685	(556)	0.22
Weight loss	6089	3.2 ± 0.1	2.52	(2.18;2.92)	< 0.001	+3.00	(0.13)	< 0.001	+22,037	(2211)	< 0.001
BED SIZE											
Small	26,976	14.0 ± 0.4	1			–			–		
Medium	49,997	26.0 ± 0.6	1.22	(1.05;1.41)	0.009	+0.08	(0.08)	0.30	+3889	(1263)	0.002
Large	115,351	60.0 ± 0.7	1.36	(1.19;1.56)	< 0.001	+0.52	(0.07)	< 0.001	+11,453	(1278)	< 0.001
OWNERSHIP OF HOSPITAL											
Government, nonfederal	17,874	9.3 ± 0.4	1			–			–		
Private, non-profit	149,417	77.7 ± 0.6	0.97	(0.83;1.12)	0.83	−0.29	(0.08)	< 0.001	799	(1798)	0.66
Private, investor-own	25,033	13.0 ± 0.4	0.88	(0.73;1.06)	0.18	−0.12	(0.09)	0.18	19,837	(1939)	< 0.001
LOCATION/TEACHING STATUS											
Rural	21,853	11.4 ± 0.4	1			–			–		
Urban, non-teaching	74,897	38.9 ± 0.7	0.98	(0.85;1.14)	0.83	+0.51	(0.06)	< 0.001	12,927	(1003)	< 0.001
Urban, teaching	95,574	49.7 ± 0.7	1.02	(0.89;1.18)	0.73	+0.90	(0.07)	< 0.001	21,308	(1343)	< 0.001
REGION OF HOSPITAL											
Northeast	31,994	16.6 ± 0.5	1			–			–		
Midwest	54,484	28.3 ± 0.7	0.98	(0.86;1.13)	0.82	−0.51	(0.07)	< 0.001	−6613	(1789)	< 0.001
South	72,882	37.9 ± 0.7	1.02	(0.90;1.16)	0.76	−0.46	(0.07)	< 0.001	−5905	(1818)	0.001
West	32,964	17.1 ± 0.5	1.09	(0.94;1.26)	0.26	−0.79	(0.09)	< 0.001	+10,847	(2562)	< 0.001
Unweighted sample	192,324			177,508			177,632			173,859	
Weighted sample	961,620			887,540			888,160			869,295	

AIDS, Acquired Immune deficiency Syndrome; CHF, Congestive Heart Failure; LOS, Length of stay; MR, mortality Risk; NIS, Nationwide Inpatient Sample; OSA, Obstructive Sleep Apnea; OSD, Other Sleep Disturbances; TC, Total Charges; Unwt, Unweighted; Wt, Weighted.

**Sample of older adults with any sleep disturbance in 2012 having complete data on each covariates entered in the model.*

we observed that the youngest-old (60–64 years) tended to have greater rates of change for both insomnia and OSA than the older age groups (65 years and older). A possible explanation for this finding is that a percentage of the oldest-old with sleep disturbances and comorbid health conditions may have died at earlier ages. Thus, a survivor effect may be occurring where the oldest-old adults with sleep disturbances are a selected group of individuals with less severe sleep disturbances and/or comorbid medical conditions. Nevertheless, a growing body of evidence has shown that (short or long) sleep duration (Cohen-Mansfield and Perach, 2012; Ensrud et al., 2012; Garde et al., 2013; Jung et al., 2013; Kakizaki et al., 2013; Kurina et al., 2013; Yeo et al., 2013; Azevedo Da Silva et al., 2014; Benito-León et al., 2014; Duggan et al., 2014; Pan et al., 2014; Rod et al., 2014; Xiao

et al., 2014; Cai et al., 2015; Hall et al., 2015), sleep disturbances (Ensrud et al., 2012; Omachi et al., 2012; Rod et al., 2014), and obstructive sleep apnea (OSA; Ge et al., 2013; Lee et al., 2013; Lockhart et al., 2013; Muraja-Murro et al., 2013; Stanchina et al., 2013; Kendzerska et al., 2014; Louis et al., 2014; Marshall et al., 2014) may predict all-cause (Seicean et al., 2011; Ensrud et al., 2012; Howrey et al., 2012; Johansson et al., 2012; Nieto et al., 2012; Omachi et al., 2012; Garde et al., 2013; Ge et al., 2013; Jung et al., 2013; Kakizaki et al., 2013; Kurina et al., 2013; Lee et al., 2013; Lockhart et al., 2013; Muraja-Murro et al., 2013; Yeo et al., 2013; Louis et al., 2014; Marshall et al., 2014; Pan et al., 2014; Rod et al., 2014; Xiao et al., 2014; Hall et al., 2015; Rahman and Adjeroh, 2015), cardiovascular- (Nieto et al., 2012; Garde et al., 2013; Ge et al., 2013; Kakizaki et al., 2013; Yeo et al., 2013; Azevedo Da Silva et al., 2014; Marshall et al., 2014; Rod et al., 2014; Xiao et al., 2014), cancer- (Yeo et al., 2013; Marshall et al., 2014; Rod et al., 2014; Xiao et al., 2014; Rahman and Adjeroh, 2015), and dementia-specific (Cai et al., 2015) mortality. Another explanation is the increased number of co-morbidities with age that are deemed more serious to report than sleep disturbances thus those diagnoses are often missed at older ages given that only 15 diagnoses are allowed for this analysis. Generally speaking, several reasons have been proposed for the increasing sleep disturbances rates including, but not limited to, the following: (1) increased number of health conditions; (2) increase in obesity rates; (3) increase in perceived stress; (4) poor sleep habits/hygiene; (5) increase in shift work; (6) increased use of electronic devices, particularly close to bedtime, a behavior that has become salient in the US, though possibly less so among older adults (Pallesen et al., 2014; Ford et al., 2015).

While in-hospital LOS and MR among admissions with sleep disturbances has decreased, TC has increased over time. Specifically, insomnia-related hospital charges have increased from $22,250 to $38,177, OSA-related hospital charges have increased from $37,561 to $46,518, and OSD-related hospital charges have increased from $18,264 to $35,450, with those trends only partly explained by age, sex and total comorbidity distribution changes over the years. In comparison to younger adults, older adults have shown to incur direct (inpatient, outpatient, pharmacy, and emergency room) charges greater than $1253 for untreated sleep disturbances, such as insomnia (Ozminkowski et al., 2007). Particularly in light of recent data suggesting poorer health outcomes and increased rates of readmission in those individuals suffering with untreated sleep disorders, increased efforts aimed at training providers delivering both the acute (inpatient) and primary/preventive health care may assist in reducing hospitalization costs. The reduction in MR and LOS may be explained by the improved in-hospital procedures to stabilize/improve health co-morbidities (e.g., hypertension and diabetes) often associated with sleep disturbances. One study partially supports this explanation, by observing that in-hospital mortality risk appeared to decline significantly in OSA patients after adjusting for health comorbidities and demographic characteristics (Lyons et al., 2015). Consequently, it is possible that increased costs may be a result of implementing a variety of in-hospital procedures for stabilizing/improving older adults' health status, especially if they have complex etiologies, including sleep disturbances and other co-morbidities, that leads to a complex case-mix requiring multifaceted interventions. The increased costs, but reduced MR and LOS, may also reflect enhanced techniques for early disease detection and copious treatment resources.

Our study observed several patient characteristic differences across the three classes of sleep disturbances. Over the last decade men tended to have higher rates for OSA, while women tend to have higher rates for insomnia. These gender differences in OSA and insomnia rates have been supported in previous studies (Ohayon et al., 2004; Wolkove et al., 2007; Salas et al., 2014). In terms of hospitalization outcomes, women with any type of sleep disturbance tended to have lower MR and lower TC than men. It is unclear what physiological, sociological, and/or psychological factors explain the gender differences in OSA, which could assist in developing an approach for improving hospitalization outcomes associated with OSA in men. However, it has been proposed that estrogen deficiency, particularly during the peri-menopausal period, may account for the higher number of women with insomnia (Ohayon et al., 2004; Wolkove et al., 2007).

Interestingly, we observed that older whites had consistently higher rates of insomnia, OSA, and OSD over the last decade than older Blacks and older Hispanics. Furthermore, older Blacks with any type of sleep disturbance appeared to have lower MR, but higher LOS compared to older Whites. Previous literature has observed mixed findings regarding the racial differences in sleep disturbance rates. While some studies have supported our findings that sleep disturbances appear to be higher in older Whites than older Blacks (Redline et al., 1997; Durrence and Lichstein, 2006), other studies have observed that sleep disturbances appear to be higher in older Blacks than older Whites (Foley et al., 1999; Ancoli-Israel et al., 2002). A potential explanation for this inconsistent finding is the different methodological approaches. The current study uses clinical diagnostic codes, such as ICD-9-CM, given by a health provider to estimate sleep disturbance; however, it is unclear what diagnostic tests were given to assess the symptoms/signs common to each sleep disturbance. Many of the previous studies have estimated sleep disturbance, particularly OSA, after participants have completed clinical evaluation, standardized questionnaires, an in-lab overnight sleep study, and/or in-home sleep testing (HST; Salas et al., 2014). Furthermore, many of the previous studies have actively recruited participants within the community, while this study is accounting for individuals in the community that sought medical care. Given Blacks are less likely than Whites to utilize health care services and/or more likely to utilize health care resources with severe symptomology (Weech-Maldonado et al., 2014), our study may be underestimating the rates of sleep disturbances and the MR associated with sleep disturbances within older Blacks. However, our finding may further provides support that sleep disturbances, particularly in Blacks, may be underdiagnosed in the health care setting (Kapur et al., 2002; Benca, 2014; Salas et al., 2014). This is corroborated with findings on income differentials in the rates of sleep disturbance, whereby for both insomnia and OSA, higher income individuals had a higher rate, suggesting higher access to

health care, particularly for OSA which requires a sleep study as opposed to insomnia which is only assessed through a clinical diagnosis and patient history.

Primary insurance also appeared to be associated with sleep disturbances. Older adults with Medicare as their primary insurance had higher rates across the classes of sleep disturbances than older adults with a different primary insurance. However, Medicare beneficiaries with any type of sleep disturbance had lower MR, lower LOS, and lower TC in comparison with some of the other primary insurance programs (i.e., Medicaid, private, and self-pay). Since there are several programs available under Medicare (e.g., Medicare Advantage program (Weech-Maldonado et al., 2014), future studies should explore differences in sleep disturbance rates and hospitalization outcomes across the Medicare plans.

Similar to previous literature, the current study found that sleep disturbances are associated with cardiovascular risk factors (e.g., diabetes, hypertension, and obesity; (Wolkove et al., 2007; Neikrug and Ancoli-Israel, 2010; Beccuti and Pannain, 2011; Lyons et al., 2015), psychiatric disorders (e.g., depression and psychoses; Wolkove et al., 2007; Kaufmann et al., 2011), neurological diagnoses (e.g., AD, dementia, Parkinson's Disease; Wolkove et al., 2007; Neikrug and Ancoli-Israel, 2010), cancer (Neikrug and Ancoli-Israel, 2010), and alcohol consumption (Wolkove et al., 2007; Neikrug and Ancoli-Israel, 2010). In addition, our results indicated an increase in the average number of health conditions over the last decade. Furthermore, our results highlighted that many co-morbidities (depression, cardiovascular risk factors, and neurological disorders) steadily increased over time, which supports a coupling linear trend between these medical conditions and sleep disturbances. These findings further support the proposed rationale that the increased number of health conditions and increased rates of particular health conditions (e.g., obesity) in the last decade is associated with the increased rates in sleep disturbances over time (Kronholm et al., 2008; Pallesen et al., 2014; Ford et al., 2015). The coupled increase trend in sleep disturbances and medical conditions may also account for the increasing in-hospital costs.

Hospital characteristics differed across the three classes of sleep disturbance. Rates for insomnia and OSD were higher in investor-owned hospitals, hospitals located in rural areas, and hospitals with smaller bed sizes. In contrast, rates for OSA were higher in non-profit hospitals, hospitals located in urban areas, and hospitals with larger bed sizes. There is only limited research on these differences in hospital characteristics as it relates to various types of sleep disturbances. It is possible that neighborhood characteristics (e.g., noise pollution, lighting, and air quality in neighborhoods near hospital) and individual characteristics (e.g., proportion of individuals below the poverty level residing near hospital) may explain these differences. Further research is warranted to understand how some of these modifiable factors may reduce the number of individuals with sleep disturbances, and the subsequent hospital costs associated with sleep disturbances.

Despite many of study strengths including national representativeness, large sample size, and availability of extensive healthcare data that allow for trends analyses, the current study is not without limitations. First, it relied on administrative database using ICD-9-CM codes. These codes may not be categorized based upon the standard diagnosis criteria for sleep disorders, which may lead to diagnosis misclassification. However, the AHRQ periodically ensures quality checks with internal and external validation. Second, discharge abstracts are de-identified, thus precluding longitudinal analyses. Third, the structure of NIS limits our ability to detect multiple admissions and/or discharges from the same condition per patient, including those with insomnia. In addition, detailed patient data are lacking such that individual medication regimens and laboratory results are missing. This precludes examining important covariates we would otherwise have included. Older adults are likely taking a number of medications. Previous research has suggested that this polypharmacy patient profile is even more prominent amongst older individuals suffering from sleep (Neikrug and Ancoli-Israel, 2010). Future research is needed to explore how the relationship between sleep disturbances and hospitalization characteristics/outcomes is explained by the number and extent of an individual's medication regimen. Fourth, NIS is limited to hospitalized patients with sleep disturbance and thus trend results may not be similar in the community. Nonetheless, sleep disturbances are often underdiagnosed and untreated, particularly within the older adult population (Groth, 2005; Wolkove et al., 2007; Neikrug and Ancoli-Israel, 2010) and thus our study's estimated rates are likely conservative. As with any retrospective administrative data analysis, there is potential for bias from missing data; however, it is unlikely that missing data will have a large effect on the results because of the large sample size of the current study. Furthermore, we were unable to compare frequencies of hospitalization between patients with and without sleep disturbance over pre-set periods of time (e.g., a month or a year).

This study observed that while rates of sleep disturbances are increasing within hospital settings, the relatively low rates may reflect that many older adults' sleep disorders remain underdiagnosed. Since older adults' sleep disturbances are associated with an increase in healthcare costs, educational interventions designed to train healthcare professionals in recognizing and effectively treating sleep disturbances may assist in reducing these healthcare expenditures.

AUTHOR CONTRIBUTIONS

AG: Study conception, literature search and review, plan of analysis, interpretation of findings, write-up of parts of the manuscript, revision of the manuscript. MB: Study conception, plan of analysis, data management, statistical analysis, interpretation of findings, write-up of parts of the manuscript, revision of the manuscript. HB: Plan of analysis, literature search, write-up of parts of the manuscript, revision of the manuscript. HL: Literature search and review, data management, revision of the manuscript. RS: Interpretation of findings, write-up of parts of the manuscript, revision of the manuscript. AZ: Plan of analysis, interpretation of findings, revision of the manuscript. CG: Literature search

and review, interpretation of findings, write-up of parts of the manuscript, revision of the manuscript. SE: Plan of analysis, data management, data acquisition, interpretation of findings, revision of the manuscript.

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Disrupted Interhemispheric Synchrony in Default Mode Network Underlying the Impairment of Cognitive Flexibility in Late-Onset Depression

*Zhenghua Hou[1], Yuxiu Sui[2], Xiaopeng Song[3] and Yonggui Yuan[1]**

[1] Department of Psychosomatics and Psychiatry, Institute of Psychosomatics, Zhongda Hospital, Medical School of Southeast University, Nanjing, China, [2] Department of Psychiatry, Affiliated Nanjing Brain Hospital of Nanjing Medical University, Nanjing, China, [3] Department of Biomedical Engineering, College of Engineering, Peking University, Beijing, China

The intuitive association between cognitive impairment and aberrant functional activity in the brain network has prompted interest in exploring the role of functional connectivity in late-onset depression (LOD). The relationship of altered voxel-mirrored homotopic connectivity (VMHC) and cognitive dysfunction in LOD is not yet well understood. This study was designed to examine the implicit relationship between the disruption of interhemispheric functional coordination and cognitive impairment in LOD. LOD patients ($N = 31$) and matched healthy controls (HCs; $N = 37$) underwent neuropsychological tests and functional magnetic resonance imaging (fMRI) in this study. The intergroup difference of interhemispheric coordination was determined by calculating VMHC value in the whole brain. The neuro-behavioral relevancy approach was applied to explore the association between disrupted VMHC and cognitive measures. Receiver operating characteristic (ROC) curve analysis was used to determine the capability of disrupted regional VMHC to distinguish LOD. Compared to the HC group, significantly attenuated VMHC in the superior frontal gyrus (SFG), superior temporal gyrus (STG), posterior cerebellar lobe (CePL) and post- and precentral gyri were observed in the bilateral brain of LOD patients. The interhemispheric asynchrony in bilateral CePLs was positively correlated with the performance of trail making test B (TMT-B) in LOD patients ($r = 0.367$, $P = 0.040$). ROC analysis revealed that regions with abnormal VMHC could efficiently distinguish LOD from HCs (Area Under Curve [AUC] = 0.90, $P < 0.001$). Altered linkage patterns of intrinsic homotopic connectivity and impaired cognitive flexibility was first investigated in LOD, and it would provide a novel clue for revealing the neural substrates underlying cognitive impairment in LOD.

Keywords: late-onset depression, voxel-mirrored homotopic connectivity, functional magnetic resonance imaging, cognitive function, cerebellum

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Edited by:
Huali Wang,
Peking University Cancer Hospital, China

Reviewed by:
Mingrui Xia,
Beijing Normal University, China
Yi-Hsuan Lee,
National Yang-Ming University, Taiwan

****Correspondence:***
Yonggui Yuan
yygylh2000@sina.com

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INTRODUCTION

Geriatric depression is a prevalent and disabling mental disorder in elderly people, often characterized by impaired cognitive function and emotional symptoms (Sheline et al., 2006; Unützer and Park, 2012). A recent longitudinal study revealed that 61% of baseline depressed patients suffered from a chronic disease duration of depression during 2 years'

of follow-up (Comijs et al., 2015). Furthermore, impaired visuospatial ability, information-processing speed, and delayed memory were persistent despite the remission of depressive symptoms after 1 year (Bhalla et al., 2006). Emerging research proposed that late-life depression (Koenig et al., 2014), especially late-onset depression (LOD), exhibit more dementia-related neuropathology, which could be regarded as an important risk factor for deterioration in Alzheimer's disease (Sierksma et al., 2010; Dillon et al., 2014; Sachs-Ericsson et al., 2014). The problem with the medication of LOD is the lack of specific, objective biomarkers to assist clinicians in establishing an individualized diagnosis and in improving specific treatment. Currently, the neural underpinnings of LOD and progressive cognitive deterioration remain poorly characterized.

In the past decade, morphological and functional magnetic resonance imaging (fMRI) studies (Chen et al., 2012; Hahn et al., 2015; Lebedeva et al., 2015) of LOD have elegantly described the abnormalities in structure and function within many different brain regions, particularly in the cognitive control network (CCN) and the default-mode network (DMN), although inconsistent results were reported. Lim et al. (2012) reported that LOD patients exhibit reduced hippocampal volumes and memory function-related cortical thickness in the superior temporal cortex, anterior/posterior cingulate cortex and dorsolateral prefrontal cortex. Our previous work also found altered amygdala, hippocampal or cortico-cerebellar functional network in resting-state fMRI (RS-fMRI) and cognitive deficits in LOD (Yue et al., 2013; Yin et al., 2015a,b). Importantly, the cognitive dysfunction and abnormalities of DMN or hippocampal sub-regional networks persisted in LOD patients even though the depressive symptoms were remitted (Wang et al., 2012, 2015c; Shu et al., 2014). Evidence that resting state networks are disrupted in LOD has invigorated attempts to understand better putative markers of illness and cognitive deficit. Illustrating the neural underpinnings of cognitive impairment in LOD is essential in prompting research on early prediction, prospective clinical identification and optimal treatment targets. However, to date, few studies have elucidated the potential neuropathological mechanisms of cognition impairment in LOD.

Specifically, the disrupted information integrities between bilateral brains play a critical role in the pathophysiology of cognitive dysfunction (Zuo et al., 2010; Kourtidou et al., 2013; Wang et al., 2015b). Recent research has detected stronger amygdalar interhemispheric connectivity (Irwin et al., 2004) and decreased corpus callosum volume (Hahn et al., 2015) involving inter-hemispheric communication and cognitive function in depression. Utilizing the approach of voxel-mirrored homotopic connectivity (VMHC), which reflects the correlation of the synchrony of spontaneous brain functional activities between symmetrical regions in bilaterally hemispheric architecture (Salvador et al., 2005), researchers identified abnormal VMHC in several regions that were associated with clinical features in major depressive disorder (MDD; Lai and Wu, 2014; Wei et al., 2014). Specifically, Hermesdorf et al. (2016) detected interhemispheric asynchrony in DMN regions (e.g., precuneus, insula, etc.) in MDD. Meanwhile, recent studies and our previous results suggested that the changed network processes in DMN were related to the impairment of cognitive performance, and the balance in DMN, CCN and salience network processes are essential to maintain optimal cognitive function (Wu et al., 2013; Beason-Held et al., 2016). It is feasible to study the potential correlation between VMHC in DMN and cognitive dysfunction, for it provides a new perspective for understanding the role of DMN in the process of cognitive decline in LOD. However, to our knowledge, there are no studies investigating the possible relationship between the altered interhemispheric coordination in DMN and cognitive impairment in LOD patients.

The purpose of the present study was to explore the intrinsic difference of interhemispheric coordination between LOD patients and healthy subjects. Based on the abovementioned results, we sought to determine if regional disruption of VMHC in the prefrontal cortex, temporal gyrus, cerebellum or other DMN regions might exert an adverse impact on cognitive function. We hypothesized that the disrupted VMHC in regions of DMN would generate synergetic effects in the pathogenesis of cognitive dysfunction in LOD patients. Furthermore, we identified the performance of aberrant patterns of homotopic connectivity in distinguishing LOD patients from healthy controls (HCs).

MATERIALS AND METHODS

Participants

All participants were recruited from the Affiliated Brain Hospital of Nanjing Medical University, China. All subjects were interviewed in a semi-structured interview included in the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P), Clinician Version (First et al., 1997), and the diagnoses were determined by a consensus of at least two trained and senior psychiatrists. All participants also underwent diagnostic evaluations including clinical interview, review of medical history and demographic inventory. The participants met the following inclusion criteria: (1) they met the major depressive disorder in DSM-IV criteria at the time point of enrollment; (2) they were in their first depressive episode and the age of onset was over 55 years; (3) 17 items Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) were greater than 17; (4) absence of another major psychiatric illness, including substance abuse or dependence; (5) absence of primary neurological illness, including dementia or stroke; (6) absence of severe medical illness that impair cognitive function obviously; (7) no history of receiving electroconvulsive therapy; (8) T2-weighted MRI of all patients did not show severe white matter impairment such as infarction or other vascular lesions; (9) have no psychotic symptoms (i.e., hallucination/bizarre delusions/thought broadcasting); (10) without taking antidepressant and within 6 months prior to the MRI scan. The inclusion criteria for HCs are similar to LOD patients except, meeting the diagnostic criteria for MDD and HAMD-17 score which was greater than 17, and with no

first-degree family history of psychiatric illness. All subjects were unequivocally and naturally right-handed. Thirty-one LOD patients and 37 HCs were recruited in this study. The Nanjing Medical University Research Ethics Committee approved the study and written informed consent was obtained from all participants.

Neuropsychological Measurements

All subjects underwent diagnostic evaluations, including the HAMD, and cognitive function testing with a neuropsychological battery that consisted of the Mini-Mental State Examination (MMSE), the Auditory Verbal Learning Test (AVLT)-delayed recall, the Digit Span Test (DST-forward and backward), the Symbol Digit Modalities Test (SDMT), the Verbal Fluency Test (VFT-animal and verb) and the Trail Making Test (TMT-A and B).

Image Acquisition and Processing

All subjects underwent the MRI scans at the Affiliated Nanjing Brain Hospital of Nanjing Medical University. The subjects were scanned using a Siemens 3.0 Tesla scanner with a homogeneous birdcage head coil. Subjects lay supine with the head snugly fixed by a belt and foam pads to minimize head motion. A gradient-recalled echo-planar imaging (GRE-EPI) pulse sequence was set up to acquire resting-state images. The acquisition parameters of RS-fMRI were as follows: repetition time = 2000 ms; echo time = 30 ms; flip angle = 90°; acquisition matrix = 64 × 64; field of view = 240 mm^2 × 240 mm^2; thickness = 4.0 mm; gap = 0 mm; 31 axial slices and 3.75 mm^2 × 3.75 mm^2 in-plane resolution parallel to the anterior commissure-posterior commissure line. High-resolution T1-weighted axial images covering the whole brain were acquired utilizing a 3-dimensional inversion recovery prepared fast spoiled gradient echo (SPGR) sequence presented as follows: repetition time = 1900 ms; echo time = 2.48 ms; flip angle = 9°; acquisition matrix = 256 × 96; field of view = 250 mm × 200 mm; thickness = 1.0 mm; gap = 0 mm. Those above acquisition sequences generated 140 volumes in 7 min 6 s and 128 slices in 4.3 min, respectively. All subjects were guided to keep their eyes closed and to relax, to remain awake and not to think anything specific during scanning.

Functional Image Processing

Functional images were preprocessed utilizing the Data Processing Assistant for Resting-State Function (DPARSF 2.3 Advanced edition) MR Imaging toolkit (Yan and Zang, 2010), which synthesizes procedures based on the Resting-State Functional MR imaging toolkit (REST[1]; Song et al., 2011), and statistical parametric mapping software package (SPM8[2]). The first 10 time points were discounted in order to ensure stable-state longitudinal magnetization and adaptation to inherent scanner noise. The remaining 130 RS-fMRI images were sequentially performed according to the following steps: (1) slice timed with the 31st slice as a reference slice; corrected for temporal differences and head motion correction (participants with head motion of more than 1.5 mm of maximum displacement in any direction (x, y, or z) or 1.5° of angular motion were excluded from the present study); (2) coregistered T1 to functional image and then reoriented; (3) for spatial normalization, T1-weighted anatomic images were segmented into white matter, gray matter and cerebrospinal fluid, and then normalized to the Montreal Neurological Institute space by using the transformation parameters estimated using a unified segmentation algorithm (Ashburner and Friston, 2005). The above transformation parameters were applied to the functional images and then the functional images with isotropic voxels of 3 mm resampled; (4) spatial smoothing undertaken with a 6 mm full-width at half-maximum isotropic Gaussian kernel; (5) the linear trend within each voxel's time series removed; (6) nuisance signals (white matter, cerebrospinal fluid signals, head-motion parameters calculated by rigid body six correction) and spike regressors regressed out; (7) temporal bandpass (0.01–0.08 Hz) to minimize low-frequency drift and high-frequency noise filtered.

[1]http://www.restfmri.net
[2]http://www.fil.ion.ucl.ac.uk/spm

Voxel-Mirrored Homotopic Connectivity

For the calculation of VMHC value in the geometric configuration of the cerebral hemispheres, the preprocessed functional images were transformed to a symmetric space conforming to the following procedure: (1) generated a mean image by averaging the normalized gray matter images for all subjects; (2) averaged the above mean image with bilateral mirrored version to create a group-specific symmetrical template; (3) registered every individual normalized gray matter image to the generated symmetric template, and then transformed the functional images based on the nonlinear strategy.

Subsequently, Pearson's correlation analysis was conducted between each pair of time series within symmetrical interhemispheric voxels. The computed correlation coefficients were Fisher z-transformed to obtain a VMHC z-map for statistical analyses. For the clusters with significant differences, mean VMHC values were extracted for further analyses. The details of VMHC acquisition have been elucidated in a previous study (Zuo et al., 2010). In order to verify the reproducibility and robustness of the VMHC differences between LOD patients and HCs in the present study, the split-half validation approach was adopted. We randomly selected $N = 16$ LOD patients and $N = 18$ HCs from the initial sample and then performed the two-sample t-tests with age, gender, education and GMV as covariates.

Statistical Analyses

Independent-sample t-test, Chi-squared test or Analysis of covariance (Statistical Package for the Social Sciences software, SPSS17.0, Chicago, IL, USA) was used to determine significant differences in demographic data, HAMD scores and neuropsychological performance between LOD and HCs. The Cohen's d values that reflect the effective size of the statistical difference between groups was calculated by G*Power software 3.1 (Faul et al., 2007). For comparing of

TABLE 1 | Demographic and clinical characteristics of LOD and HCs.

Items	LOD ($n = 31$)	HCs ($n = 37$)	Cohen's d	Statistic value	P value
Gender (male: female)	10:21	18:19	/	$\chi^2 = 2.12$, df = 1	0.15[a]
Age (years)	68.00 ± 6.09	65.27 ± 7.52	/	$t = 1.62$, df = 66	0.11[b]
Education level (years)	9.52 ± 4.21	12.84 ± 3.04	0.90	$t = -3.66$, df = 66	0.000[b]
HAMD	31.42 ± 4.44	2.03 ± 2.33	8.29	$F = 602.42$, df = 2	0.000[c]
MMSE	28.23 ± 1.94	29.46 ± 0.93	0.81	$F = 6.62$, df = 2	0.002[c]
SDMT	17.16 ± 5.64	38.70 ± 10.16	1.50	$F = 65.34$, df = 2	0.000[c]
AVLT-delayed recall	10.84 ± 0.82	11.57 ± 0.69	0.96	$F = 8.37$, df = 2	0.001[c]
VFT	25.35 ± 6.66	39.00 ± 8.46	1.79	$F = 27.66$, df = 2	0.000[c]
DST	10.52 ± 1.55	13.54 ± 1.79	1.80	$F = 32.73$, df = 2	0.000[c]
TMT-A (s)	107.86 ± 30.78	74.59 ± 22.38	1.24	$F = 21.68$, df = 2	0.000[c]
TMT-B (s)	183.31 ± 49.89	144.27 ± 45.59	0.82	$F = 14.90$, df = 2	0.001[c]

Abbreviation: LOD, late-onset depression; HCs, healthy controls; HAMD, Hamilton Depression Scale; MMSE, Mini Mental State Exam; SDMT, Symbol Digit Modalities Test; AVLT-delayed recall, Auditory Verbal Learning Test-delayed recall; VFT, Verbal Fluency Test-animal and verb; DST, Digit Span Test-forward and backward; TMT-A, Trail Making Test-A; TMT-B, Trail Making Test-B. Parametric values are represented as the Mean ± SD (standard deviation). [a]Chi-square test. [b]Independent-samples t-test. [c]Analysis of covariance.

TABLE 2 | The decreased regional VMHC in LOD group relative to HCs.

Brain regions	BA	Voxel number	Coordinates MNI			T-score
			X	Y	Z	
LOD < HCs:						
Superior frontal gyrus	10	100	6	21	57	−5.34
Superior temporal gyrus	22	74	51	−6	3	−5.46
Cerebellum posterior lobe	/	117	45	−63	−36	−5.13
Postcentral gyrus	2/3	65	27	−24	66	−4.95
Precentral gyrus	4	56	17	−29	73	−5.07

Abbreviations: VHMC, Voxel-Mirrored Homotopic Connectivity; LOD, Late-Onset Depression; HCs, Healthy Controls; BA, Brodmann Area; MNI coordinates, Montreal Neurological Institute coordinates of the peak voxel; T, the statistical value of the peak intensity voxel; 1 voxel = 3 mm × 3 mm × 3 mm. The MNI coordinates of peak voxel are symmetrical as the VMHC computation bases on the symmetrical template.

imaging data, the whole brain gray matter volume, age, gender and education level were used as covariates, the between-group differences of VMHC were calculated in REST and the results were multiple corrected with AlphaSim analysis as determined by Monte-Carlo simulation (threshold has been set at $P < 0.001$, corrected with voxel-level $P < 0.01$, cluster size: ≥55 voxels, see Analysis of Functional NeuroImages [AFNI][3]) within the unilateral hemisphere of the symmetric template. The continuous variables are presented as mean ± Standard Deviation (SD). The relationships between VMHC changes and characteristic of depression in patients were examined by bivariate Pearson's correlation analysis. We calculated the predictive performance of the altered VMHC values using sensitivity, specificity and area under the receiver operating characteristic (ROC) curves (Area Under Curve [AUC]: 0.9–1.0 = excellent; 0.8–0.9 = well; 0.7–0.8 = fair; 0.6–0.7 = poor; 0.5–0.6 = fail). Optimal cut-off between sensitivity and specificity were determined by maximizing the Youden's index J (J = sensitivity + specificity − 1). Binary Logistic regression analysis was performed to integrate the combined distinguishing effect of brain regions with altered VMHC. The threshold of statistical significance was defined as $P < 0.05$.

[3]http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf

RESULTS

Demographic and Neuropsychological Data

Demographic and clinical characteristics of LOD and HCs were showed in **Table 1**, there were significant differences ($P < 0.005$) in years of education and cognitive performance but not in gender distribution ($\chi^2 = 2.12$, $P = 0.15$) and age ($t = 1.62$, $P = 0.11$). Compared to HCs, LOD group exhibited poor cognitive performance in extensive domains. As an additional statistical control, we presented results by controlling education level, age and gender.

Voxel-Mirrored Homotopic Connectivity Data

Compared to the HCs, the LOD group showed significant low interhemispheric homotopic coordination in the superior frontal gyrus (SFG), superior temporal gyrus (STG), posterior cerebellar lobe (CePL) and postcentral and precentral gyri (**Table 2**, **Figure 1**). No brain regions with higher VMHC were detected between two groups. By split-half sample validation, the regions of lower VMHC were confirmed in the CePL, postcentral and precentral gyri (**Figure 2**), which were highly in line with the results from the full sample.

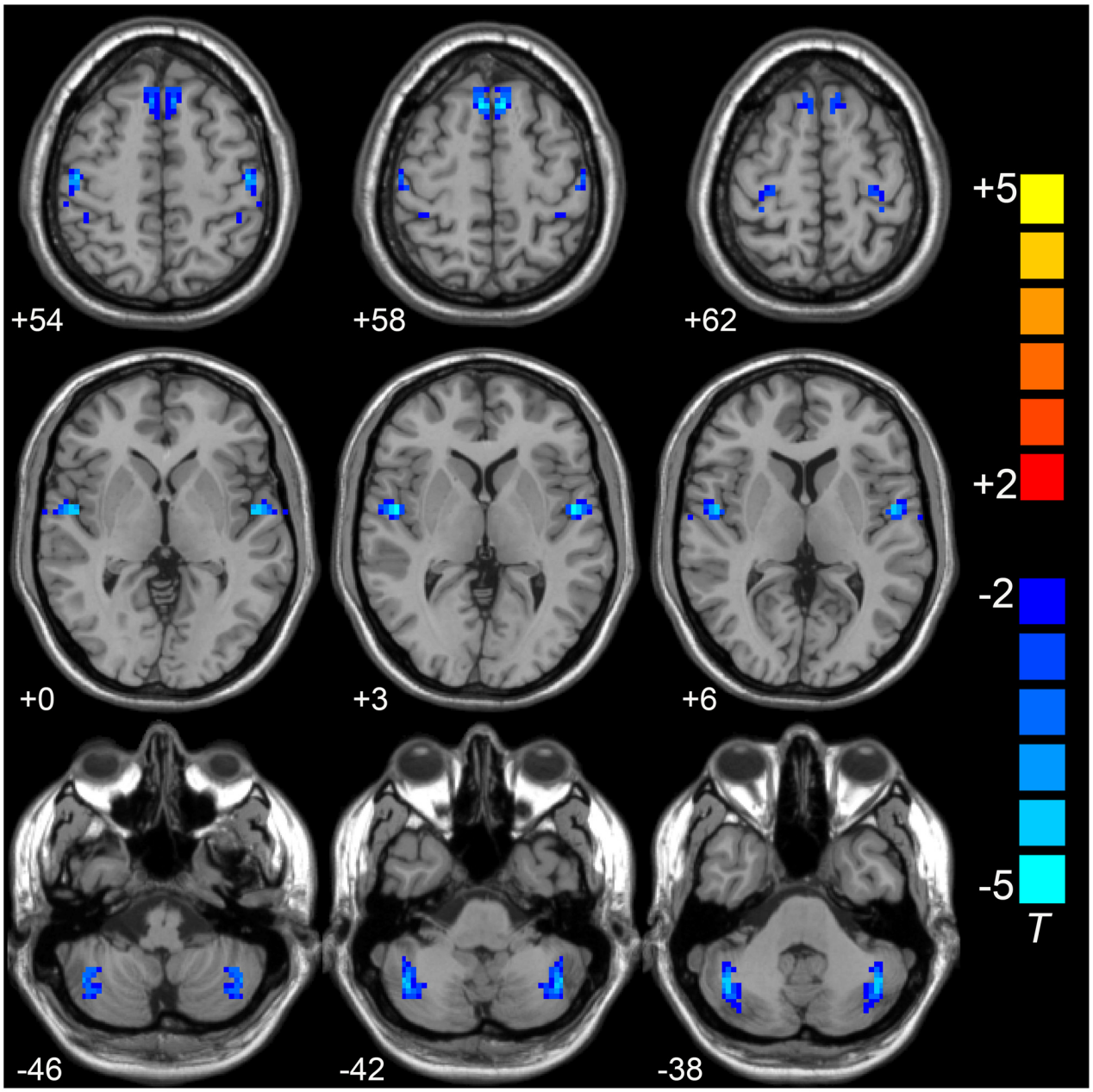

FIGURE 1 | Compared to HCs group,VMHC in superior frontal gyrus (SFG), superior temporal gyrus (STG), posterior cerebellar lobe (CePL), postcentral and precentral gyri was observed in LOD. Blue color represents reduced VMHC value in LOD. The numbers at the down left of each image refer to the z-coordinates in Montreal Neurological Institute template. The threshold was set at a corrected $P < 0.001$ (corrected with $P < 0.01$ for each voxel and cluster volume ≥55 voxels) and the *t*-score bar is present at the right-side. Notes: HCs, Healthy Controls; VMHC, Voxel-Mirrored Homotopic Connectivity; LOD, Late-Onset Depression.

Neuro-Behavioral Relevancy Analysis Between VMHC and Neuropsychological Variables

Pearson's correlation analysis suggested that the reduced VMHC strength in bilateral CePL was positively correlated with the performance of TMT-B in LOD patients ($r = 0.367$, $P = 0.040$). No significant relationship was confirmed in the LOD or HC groups between the VMHC in other brain regions and the neuropsychological variations (**Figure 3**).

The Diagnostic Performance of Altered VMHC in Differentiating LOD from HCs

ROC analysis demonstrated that the regional VMHC changes of CePL (AUC = 0.853, $P < 0.001$), SFG (AUC = 0.845, $P < 0.001$),

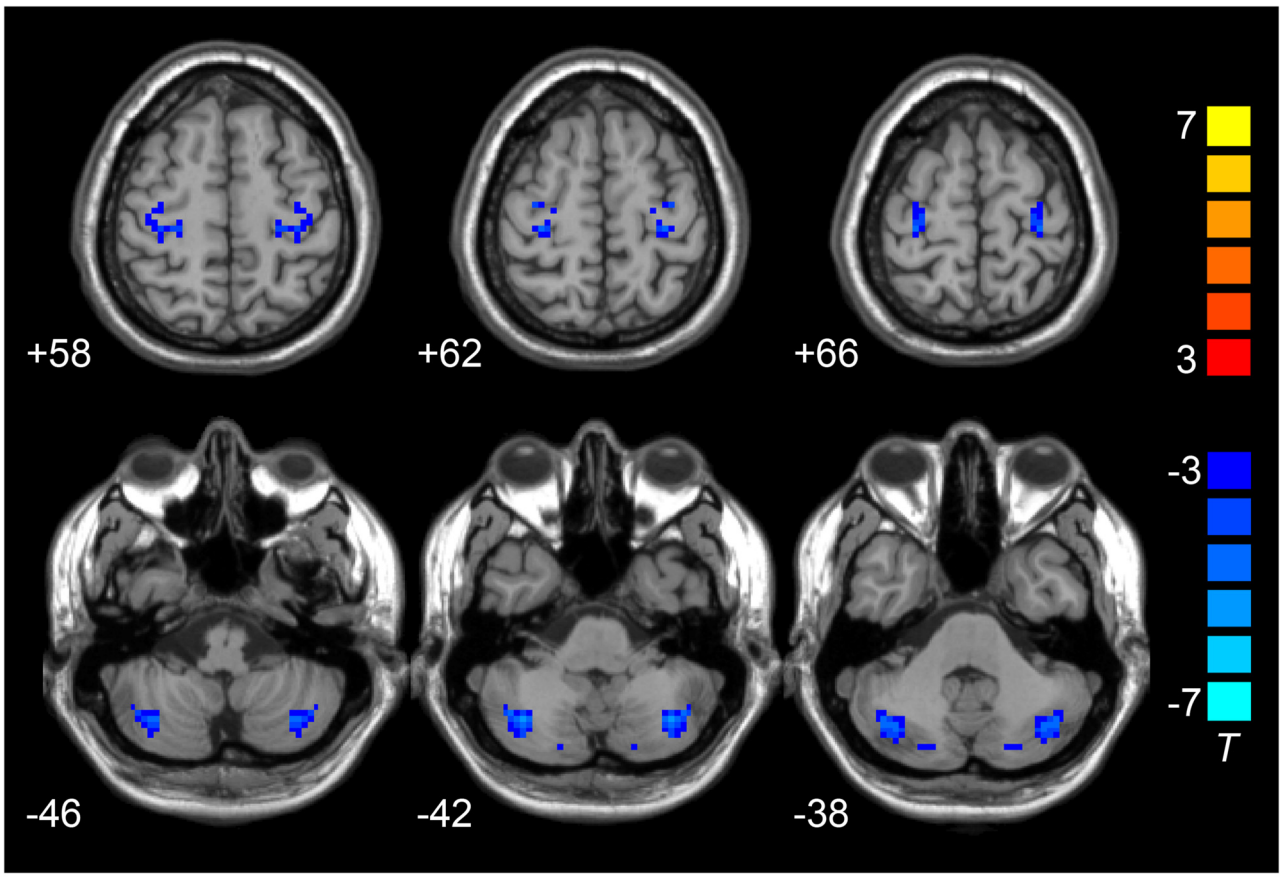

FIGURE 2 | Results of split-half sample validation. Comparisons of VMHC were analyzed between 16 LOD and 18 HCs. Blue color represents reduced VMHC value in LOD. The numbers at the down left of each image refer to the *z*-coordinates in Montreal Neurological Institute template. The threshold was set at a corrected $P < 0.001$ (corrected with $P < 0.01$ for each voxel and cluster volume ≥55 voxels) and the *t*-score bar is present at the right-side. Notes: HCs, Healthy Controls; VMHC, Voxel-Mirrored Homotopic Connectivity; LOD, Late-Onset Depression.

STG (AUC = 0.864, $P < 0.001$) and postcentral gyrus (PoCG) (AUC = 0.840, $P < 0.001$) exhibited good performance in distinguishing LOD patients from HCs. Moreover, when the combined effects of these regional changes were taken into account, the outstanding differentiated ability (AUC = 0.896, $P < 0.001$) was achieved with balanced sensitivity (84%) and specificity (73%; **Figure 4**).

DISCUSSION

In the present study, we first examined the differences of resting-state voxel-wise VMHC and the possible interaction with cognitive performance in LOD patients and HCs. For LOD patients, significantly decreased VMHC were observed in bilateral STG, post- and precentral gyri, SFG and CePL as compared with HCs. Compatible with previous studies, the overall cognitive performance (as assessed by MMSE) or specific domains of cognition (i.e., TMT, SDMT) significantly declined in healthy subjects (Richard-Devantoy et al., 2013; Sachs-Ericsson et al., 2013). Furthermore, the novel pattern of positive correlation between disrupted homotopic coordination (decreased VMHC) in CePL and total completion time on TMT-B was confirmed in this study. Importantly, these altered regional VMHC showed good performance in differentiating LOD patients from HCs.

Evidence from neuroimaging studies concerning STG and post/precentral gyri have yielded conflicting results. A regional homogeneity study reported significantly increased spontaneous neural activity in both the left STG and right PoCG (Liu et al., 2012), whereas other research demonstrated the decreased activity coherence in the PoCG in elderly depressed patients (Ma et al., 2013). A recent coordinate-based meta-analysis highlighted increased activation in the left precentral gyrus and right superior temporal with reduced activity in the right precentral gyrus during working memory tasks (Wang et al., 2015a). Furthermore, increased activation was observed in the right precentral gyrus that underlies dysfunctional cognitive processing during semantic verbal fluency in depression (Backes et al., 2014). Additionally, the decreased interhemispheric coordination in STG was found in treatment-resistant depression (Guo et al., 2013). STG and post/precentral gyri accounted for language processing and motor supplementary, respectively

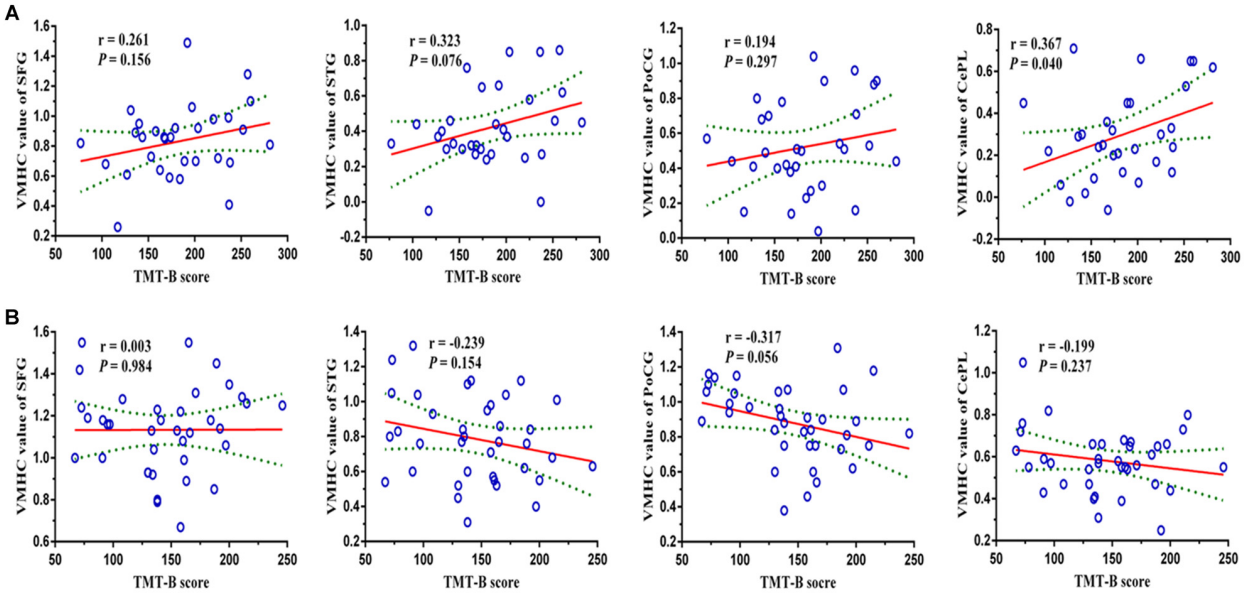

FIGURE 3 | Pearson's correlation analysis revealed that the reduced VMHC strength in bilateral CePL was positively correlated with the performance of TMT-B in LOD ($r = 0.367$, $P = 0.040$). Notes: VMHC, Voxel-Mirrored Homotopic Connectivity; SFG, Superior Frontal Gyrus; STG, Superior Temporal Gyrus; PoCG, Postcentral Gyrus; CePL, Posterior Cerebellar Lobe; TMT-B, Trail Making Test B; LOD, Late-Onset Depression. The figures of row **(A,B)** represent the relationships (TMT-B and regional VMHC values) in LOD and HCs, respectively.

and were critical for executive and social function (Kana et al., 2015; Roux et al., 2015; Upadhyay et al., 2016). The reduced VMHC of STG and post/precentral gyri in the present study may disrupt the integration of bilateral brain function when dealing with an emotional event or cognitive task. As a core component of DMN, SFG is involved in the process of emotion and cognition, including self-referential processing, learning function, episodic memory and working memory processing (Bai et al., 2011; Coutinho et al., 2016). The atrophy and disrupted white matter integrity of SFG was proposed to be a marker of disease severity and impending cognitive decline in late-life depression (Reppermund et al., 2014; Boccia et al., 2015). Furthermore, the volumetric alteration in SFG was correlated with numerical daily function, including working memory and abstract reasoning (Benavides-Varela et al., 2015). Our previous work also demonstrated that the abnormal intrinsic activity in SFG was related to cognitive dysfunction in LOD (Yue et al., 2015). Specifically, in the present study, the disrupted interhemispheric coordination in bilateral SFG may be representative of poor cognitive control regulating the default mode in the processing of emotional reaction, further supporting the viewpoint that impairment in the neural network led to an increased susceptibility to early cognitive deficit in LOD. The notable effect of altered regional VMHC (STG, postcentral gyri, SFG and CePL) in differentiating LOD was also primarily confirmed in this study. The distinct performance identified in the ROC indicated that the combined VMHC change of several brain regions rather than that of a single region can be more accurate in distinguishing the LOD patients from HCs. Those synthetical results further suggest that the neural activities in those bilateral brain regions were desynchronized in LOD patients with cognitive impairment. In sum, the disrupted homotopic connectivity in these regions

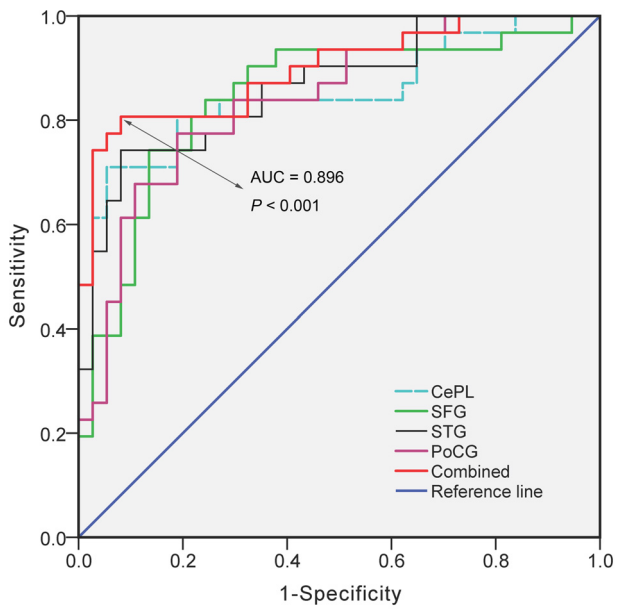

FIGURE 4 | The diagnostic performance of disrupted VMHC in differentiating LOD from HCs. Notes: VMHC, Voxel-Mirrored Homotopic Connectivity; LOD, Late-Onset Depression; HCs, Healthy Controls; CePL, Posterior Cerebellar Lobe; SFG, Superior Frontal Gyrus; STG, Superior Temporal Gyrus; PoCG, Postcentral gyrus; AUC, Area Under Curve.

may assist in the diagnostic decision and early intervention of LOD as well as the identification of potential conversion to dementia.

Intriguingly, the novel positive relationship between reduced VHMC in bilateral cerebellum posterior lobes and TMT-B score was detected in the present study. Generally, completion time on TMT-B is considered to constitute a behavioral estimate of the capacity of cognitive flexibility, attributed to the function of frontal lobes. Using voxel-based lesion-behavior mapping, the right hemispheric frontal lesions were reported to be associated with TMT-B score (Kopp et al., 2015). Traditionally, the cerebellum is thought to account for body balance and sensomotor function. The cerebellum has anatomically reciprocal connections with the cerebral cortex and limbic regions involved in complex cognitive operation and emotional processing (Stoodley and Schmahmann, 2009, 2010). The volumetric cerebellum reduction was observed in depression (Grieve et al., 2013), and the aberrant cortico-cerebellar functional networks were associated with impaired episodic memory and emotional regulation (Balsters et al., 2014). Additionally, Lai and Wu (2014) reported that the weaker interhemispheric coordination between bilateral CePL probably represented the disturbed function of the emotional and cognitive process. It should be noted that no evidence was proposed to the linkage between altered VMHC within bilateral cerebellum and cognitive impairment in LOD. The present results indicated that the depressive state might influence the interhemispheric information communication for cognitive processing, and the neural circuitry modulating cognition was pivotal as scaffolding to mediate adverse emotion effect. The underlying mechanisms of these abnormal coordination across bilateral hemispheres in resting state are still unclear and deserve further investigation.

There were methodological considerations and limitations in the present study that must be acknowledged. First, by lacking follow-up data, we couldn't determine the discrepancy of VMHC with time-related trajectory between LOD patients and HCs across the aging process. Cortical atrophy is also a potential factor that might impact the homotopic coordination in our study. Second, the education level between the LOD patients and HCs in this study was not well matched, even though we controlled the bias by the statistical method; future work with homogeneous participants would help verify whether the findings are common. Finally, the results of this study only stem from the single modality of rs-fMRI; it should benefit by utilizing optimized analytical strategies and multiple imaging modalities (e.g., white matter fiber-tracking) to understand the structural substrate underlying the VMHC alteration. Future works with longitudinal design, data analyses of multiple modalities imaging, and well-matched subjects are warranted to replicate and validate these findings.

Collectively, our study was designed as a pragmatic work to explore the potential alterations of integrative processing and information communication in LOD with cognitive deficit. The relationship between abnormal VMHC strength and cognitive dysfunction was first explored in LOD. It will likely shed further light on the permanency of neuropathological traits in the deterioration of dementia. The results of differentiated regional VMHC changes indicate that the neuroimaging-guided differential diagnosis could serve as promising neural targets for personalized diagnosis and optimal treatment in future clinical practice.

AUTHOR CONTRIBUTIONS

ZH recruited the participants, collected the data, performed data analyses and prepared the manuscript. XS helped with data analyses and reviewed the manuscript. YS helped with patients enrollment and data analyses. YY designed the study and supervised preparation of the manuscript.

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