

Effects of donepezil on the amplitude of low-frequency fluctuations in the brain of patients with Alzheimer's disease: evidence from resting-state functional magnetic resonance imaging

Hua Yang^a, Jiangtao Zhang^a and Jianan Cheng^b

Objectives To monitor the effects of donepezil on spontaneous neuronal activity (SNA), and the mechanisms underlying these effects in patients with mild-to-moderate Alzheimer's disease, using the amplitude of low-frequency fluctuations (ALFFs), a metric of resting-state functional MRI (rs-fMRI).

Methods Eleven patients with Alzheimer's disease were treated with donepezil for 6 months. Before and after treatment, the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Clinical Dementia Rating (CDR), Neuropsychiatric Inventory and Activities of Daily Living scores, along with rs-fMRI of patients were assessed. Eleven age-, sex-, and education-matched controls underwent MMSE and CDR assessments and rs-fMRI at enrollment. The ALFFs of the whole brain were obtained and compared between the groups.

Results Following donepezil treatment, MMSE scores increased ($P=0.043$) and ADAS-cog scores decreased ($P=0.010$). Regarding SNA post-treatment, ALFF increased significantly in the right triangular part of the inferior frontal gyrus (IFGtriang; $P=0.030$; $d=-0.595$) and

the right orbital part of the inferior frontal gyrus ($P=0.044$; $d=-0.628$) and decreased significantly in the left medial orbital part of the superior frontal gyrus ($P=0.039$; $d=0.606$) and the right gyrus rectus ($P=0.010$; $d=0.609$). Furthermore, the changes in ADAS-cog scores from before to after treatment were positively correlated with the changes in ALFF in the right IFGtriang ($r=0.645$; $P=0.032$).

Conclusions Donepezil improved SNA in the frontal lobe of patients with Alzheimer's disease. Therefore, ALFF was demonstrated to be a potential tool for assessing the effectiveness of Alzheimer's disease treatment. *NeuroReport* 32: 907–912 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

NeuroReport 2021, 32:907–912

Keywords: Alzheimer's disease, amplitude of low-frequency fluctuation, donepezil, resting-state functional MRI

^aDepartment of Geriatrics and ^bDepartment of Pharmacy, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang, China

Correspondence to Jiangtao Zhang, MD, Department of Geriatrics, Tongde Hospital of Zhejiang Province, 234 Gucui Road XihuDist, Hangzhou 310012, People's Republic of China
Tel: +86 571 88723128; e-mail: 649946282@qq.com

Received 20 January 2021 Accepted 31 March 2021

Introduction

Alzheimer's disease is a primary degenerative brain disease characterized by insidious onset and progressive development [1]. Its main clinical characteristics are cognitive impairment, abnormal mental behavior and decline in social functions. According to a WHO report, approximately 60 million people worldwide have Alzheimer's disease. As the population ages, the number of patients is expected to increase further.

Studies have indicated that spontaneous activity of brain neurons in Alzheimer's disease patients is significantly altered and that this disturbance can be identified years before the onset of clinical symptoms [2–4]. Spontaneous activity in brain neurons is described as the rhythmic

variation of potentials spontaneously produced by the neurons in the cerebral cortex.

Donepezil is the most commonly used cholinesterase inhibitor in clinical practice and is currently a first-line drug approved for the treatment of Alzheimer's disease in several countries. It inhibits acetylcholinesterase competitively and noncompetitively, thereby increasing acetylcholine concentration in the synaptic cleft. However, opinions vary regarding its efficacy due to the inability of donepezil to significantly improve Alzheimer's disease symptomatology. Nonetheless, donepezil treatment for Alzheimer's disease is supported by abundant medical evidence. The current research on donepezil primarily focuses on neuropharmacology, with limited studies investigating its effects on brain function. In particular, there is a lack of functional imaging-based studies investigating the spontaneous activity of brain neurons because the effect of donepezil cannot be identified in the first place.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

The amplitude of low-frequency fluctuations (ALFF) can reflect spontaneous neural activity (SNA) in the brain and represent the intensity of brain activity; its sensitivity and specificity are high, which aids in the exploration of the biological mechanisms underlying cognitive impairment [4]. ALFF reflects SNA in the local brain regions and the physiological state of the brain tissue by calculating the fluctuations of the blood oxygen level-dependent (BOLD) signal. This method is commonly used in studies on resting-state functional MRI (rs-fMRI). Studies have shown that ALFF can quickly and sensitively reflect the intensity of activity in local brain neurons. In recent years, ALFF has been widely used in studies on various mental disorders, including Alzheimer's disease and depression. This study used the ALFF calculation method based on rs-fMRI to study the effect of donepezil on the spontaneous activity of brain neurons in Alzheimer's disease patients.

Our hypotheses were as follows: (1) donepezil can induce changes in the ALFF values of the relevant brain regions in patients with Alzheimer's disease and (2) the changes in ALFF values are associated with improvements in cognitive function.

Materials and methods

Participants

A total of 22 right-handed participants, including 11 patients with Alzheimer's disease and 11 age-, sex- and education-matched healthy controls, were enrolled in this study. All patients met the diagnostic criteria for possible or probable Alzheimer's disease, as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. The diagnoses were confirmed by two senior geriatric psychiatrists. The method of administration of donepezil (produced by Eisai China Inc.) was as follows: initially, a dose of 5 mg/day was administered orally at bedtime; after 4 weeks, the dose was increased to 10 mg/day and continued until the end of the sixth month. rs-fMRI scans were performed before and 6 months after drug treatment. In addition, the cognitive function, psychobehavioral symptoms and daily living skills of the patients were assessed using the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Clinical Dementia Rating (CDR) scale, Neuropsychiatric Inventory (NPI) questionnaire and Activities of Daily Living (ADL) scale. The healthy controls were required to have normal cognitive function, no history of cerebrovascular disease or brain trauma, no significant memory decline or mood disorder, an MMSE score of >24 and a CDR score of 0. The healthy controls underwent rs-fMRI at enrollment. The healthy control did not receive donepezil or any other treatment that affected cognition. This study was approved by the ethics committee, and written informed consent was obtained from all participants.

MRI data acquisition

MRI data were acquired using a 3.0-Tesla scanner (Magnetom Verio, Siemens, Erlangen, Germany). Tight but comfortable foam padding was used to minimize head motion, and earplugs were used to reduce scanner noise. High-resolution structural images were acquired sagittally using a three-dimensional (3D) T1-weighted magnetization-prepared rapid gradient-echo sequence with the following parameters: repetition time (TR)=1900 ms, echo time (TE)=2.48 ms, inversion time (TI)=900 ms, flip angle (FA)=9°, field of view (FOV)=250 mm×250 mm, matrix=512×512, slice thickness=1 mm, no gap and slice number=176. Resting-state functional BOLD images were acquired axially using a gradient-echo echo-planar imaging sequence with the following parameters: TR/TE=2000/30 ms, FA=90°, FOV=220×220 mm, matrix=64×64, slice thickness=4 mm, gap=0.8 mm, slice number=30 and 160 volumes. All subjects were instructed to keep their eyes closed, relax, not move their heads, not fall asleep, and not do, think, or feel anything during the MRI scan. All MRI images were visually inspected to ensure that only images without visible artifacts were included in subsequent analyses.

fMRI data preprocessing

Resting-state BOLD data were preprocessed using Statistical Parametric Mapping 12 (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for rs-fMRI (DPARF, <http://rfmri.org/DPARF>) [5]. The first 10 volumes for each participant were discarded to allow the signal to reach equilibrium and to allow the participants to adapt to the scanning noise. The remaining volumes were corrected for the acquisition time delay between slices. Subsequently, realignment was performed to correct the motion between time points. Head movement parameters were computed by estimating the

Table 1 Demographic and clinical characteristics of the samples

Characteristics	Alzheimer's disease patients (n=11)	Healthy controls (n=11)	Statistics	P value
Age (years)	76.6±9.1	78.7±4.8	$t=-0.677$	0.506 ^a
Sex (female/male)	9/2	10/1	$\chi^2=0.386$	0.534 ^b
Education (years)	8.6±4.5	9.8±4.8	$t=-0.645$	0.526 ^a
CDR (baseline)	1.5±0.5	0±0	$t=9.238$	<0.001 ^a
CDR (6 months)	1.5±0.5	-	$t=0$	1 ^c
MMSE (baseline)	15.2±4.3	29.3±0.8	$t=-10.615$	<0.001 ^a
MMSE (6 months)	17.2±5.0	-	$t=2.316$	0.043 ^c
ADAS-cog (baseline)	23.2±5.5	-	-	-
ADAS-cog (6 months)	19.6±5.2	-	$t=-3.166$	0.010 ^c
NPI (baseline)	7.7±11.8	-	-	-
NPI (6 months)	3.1±9.0	-	$t=-2.011$	0.072 ^c
ADL (baseline)	39.8±10.5	-	-	-
ADL (6 months)	39.6±11.5	-	$t=0.976$	0.352 ^c

The data are shown as the mean±SD. Dashes indicate no data available.

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL, Activity of Daily Living Scale; CDR, clinical dementia rating; MMSE, mini-mental state examination; NPI, Neuropsychiatric Inventory.

^aThe P values were obtained by two-sample t-tests.

^bThe P value was obtained by Pearson Chi-square test.

^cThe P value was obtained by paired t-test compared with baseline.

translation in each direction and the angular rotation on each axis for each volume. All participants' BOLD data were within the defined motion thresholds (i.e. translational or rotational motion parameters less than 3 mm or 3°). We also calculated frame-wise displacement, which indexes the volume-to-volume changes in head position. Several nuisance covariates (the estimated motion parameters based on the Friston-24 model, linear drift, white matter signal and cerebrospinal fluid signal) were regressed out from the data. Recent studies have reported that the signal spike caused by head motion significantly contaminated the final rs-fMRI results, even after regressing out the linear motion parameters [5,6]. Therefore, we further regressed out spike volumes when the frame-wise displacement of the specific volume exceeded 0.5. The datasets were then band-pass filtered in a frequency range of 0.01–0.1 Hz. In the normalization step, individual structural images were first coregistered with the mean functional image. Subsequently, the transformed structural images were segmented and normalized to the Montreal Neurological Institute (MNI) space using a high-level nonlinear warping algorithm; that is, they were subjected to the diffeomorphic anatomical registration through the exponentiated Lie algebra technique [7]. Finally, each filtered functional volume was spatially normalized to the MNI space, using the deformation parameters estimated during the above step, and resampled into a 3-mm cubic voxel. After normalization, all data sets were spatially smoothed with a Gaussian kernel of 6×6×6 mm full-width at half-maximum.

Amplitude of low-frequency fluctuations calculation

The ALFF was calculated according to a previous study [8]. The preprocessed time series were transformed to a frequency domain using a fast Fourier transform, and the power spectrum was obtained subsequently. Because the power of a given frequency is proportional to the square of the amplitude of this frequency component in the original time series in the time domain, the square root was calculated at each frequency of the power spectrum, and the averaged square root was obtained across 0.01–0.1 Hz at each voxel. This averaged square root was considered as the ALFF. For standardization purposes, the ALFF of each voxel was divided by the global mean ALFF value of a certain subject. To define the regions of interest (ROI), the whole brain was segmented into 90 (45 per hemisphere) cortical and subcortical regions by employing an automated anatomical labeling (AAL) template [9]. For each subject, the normalized ALFF value of each region was extracted and used for ROI-based analyses.

Statistical analysis

All statistical analyses were performed using the SPSS 19.0 software package (SPSS, Chicago, Illinois, USA). Age, education, baseline CDR and MMSE were compared between patients with Alzheimer's disease and healthy controls by using a two-sample *t*-test. Group

differences in sex were tested using Pearson's chi-square test. For patients with Alzheimer's disease, paired *t*-tests were used to evaluate changes in CDR, MMSE, ADAS-cog, NPI and ADL before and after treatment.

For ROI-based analyses of ALFF, we performed a two-sample *t*-test and effect size to explore inter-group differences between patients with Alzheimer's disease and healthy controls. Moreover, for the patient group, paired *t*-tests were used to test changes in ALFF in each ROI before and after treatment. Finally, Pearson's correlation analyses were performed in patients with Alzheimer's disease to examine the association between significant changes in ALFF and significant alterations in clinical scores following treatment. For these analyses, the levels of significance were set at $P < 0.05$, without correction for multiple comparisons because of the small sample size in the current study.

This study is an explorative study and we interpret our findings entirely descriptively.

Results

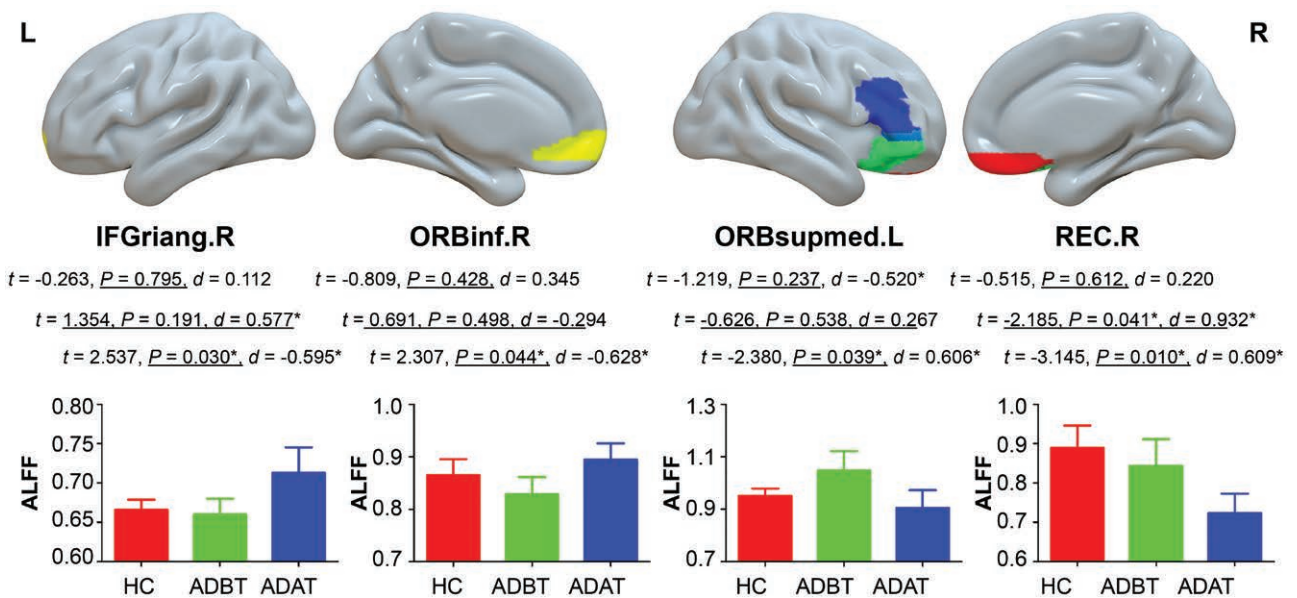
Sample characteristics

The demographic and clinical data of the sample are shown in Table 1. Specifically, the two groups did not differ in age (two-sample *t*-test, $t = -0.667$; $P = 0.506$), sex (chi-square test, $\chi^2 = 0.386$; $P = 0.534$) and education (two-sample *t*-test, $t = -0.645$; $P = 0.526$). Patients with Alzheimer's disease showed significantly higher baseline CDR (two-sample *t*-test, $t = 9.238$; $P < 0.001$) and lower baseline MMSE scores (two-sample *t*-test, $t = -10.615$; $P < 0.001$) than did the healthy control. Following treatment, patients with Alzheimer's disease exhibited significantly higher MMSE scores (paired *t*-test, $t = 2.316$; $P = 0.043$) and lower ADAS-cog scores (paired *t*-test, $t = -3.166$; $P = 0.010$) (Table 1). However, patients with Alzheimer's disease showed no significant changes in CDR (paired *t*-test, $t = 0$; $P = 1$), NPI (paired *t*-test, $t = -2.011$; $P = 0.072$) and ADL scores (paired *t*-test, $t = 0.976$; $P = 0.352$) after treatment.

Changes in amplitude of low-frequency fluctuations

Following treatment, patients with Alzheimer's disease exhibited increased ALFF in the right triangular part of the inferior frontal gyrus (IFGtriang) ($P = 0.030$; $d = -0.595$) and right orbital part of the inferior frontal gyrus (ORBinf) ($P = 0.044$; $d = -0.628$) and decreased ALFF in the left medial orbital part of the superior frontal gyrus (ORBsupmed) ($P = 0.039$; $d = 0.606$) and right gyrus rectus (REC) ($P = 0.010$; $d = 0.609$) (Fig. 1). After treatment, patients with Alzheimer's disease showed lower ALFF in the right REC ($P = 0.041$; $d = 0.932$) than did the healthy controls; however, ALFF in the right IFGtriang ($P = 0.795$; $d = 0.112$) and right ORBinf ($P = 0.428$; $d = 0.345$) did not differ between patients with Alzheimer's disease and healthy controls (Fig. 1). In addition, ADAS-cog score change was positively correlated

Fig. 1



Changes in amplitude of low-frequency fluctuations between pre- and post-treatment measurements and between patients and controls. Error bars represent standard errors. ALFF, amplitude of low-frequency fluctuations; ADBT, patients with Alzheimer's disease before treatment; ADAT, patients with Alzheimer's disease after treatment; HC, healthy controls; IFGtriang, triangular part of inferior frontal gyrus; ORBinf, orbital part of inferior frontal gyrus; L, left; ORBsupmed, medial orbital part of superior frontal gyrus; R, right; REC, gyrus rectus.

Table 2 Correlations between amplitude of low-frequency fluctuations changes and clinical score alterations following treatment^a

Regions	MMSE	ADAS-cog
Right IFGtriang	-0.546 (0.082)	0.645 (0.032)^a
Right ORBinf	-0.120 (0.725)	-0.031 (0.928)
Left ORBsupmed	0.021 (0.952)	0.145 (0.671)
Right REC	-0.021 (0.951)	-0.015 (0.964)

ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; IFGtriang, triangular part of inferior frontal gyrus; MMSE, Mini-Mental State Examination; ORBinf, orbital part of inferior frontal gyrus; ORBsupmed, medial orbital part of superior frontal gyrus; REC, gyrus rectus.

^aThe data are shown as the Pearson's correlation coefficient *r* (*P* value).

with ALFF alteration in the right IFGtriang in patients with Alzheimer's disease ($r=0.645$; $P=0.032$); however, no other significant correlations were found in this study ($P>0.05$) (Table 2).

Discussion

Our study confirmed our hypotheses that donepezil treatment led to an increase in MMSE score and a decrease in ADAS-cog score in patients with Alzheimer's disease, which corroborated the findings of previous reports [10]. In addition, changes in ALFF values were observed in multiple functional brain regions of the prefrontal lobe. Specifically, the ALFF values in the right IFGtriang and the right ORBinf increased significantly, whereas those in the left ORBsupmed and the right REC decreased significantly. Furthermore, the changes in ADAS-cog scores were positively correlated with changes in ALFF

values in the right IFGtriang of patients with Alzheimer's disease.

The IFGtriang and ORBinf are important components of the IFG that are responsible for auditory pattern perception and spatial processing of auditory signals [11]. Together, they govern language comprehension [12,13]. The IFG plays a critical role in emotional and cognitive control. The present study found that the ALFF values in the right IFGtriang and right ORBinf of donepezil-treated patients with Alzheimer's disease increased significantly and that the changes in ADAS-cog score were positively correlated with the ALFF changes in the right IFGtriang of patients with Alzheimer's disease. These findings indicated that donepezil improved SNA in these brain regions. These changes in SNA were sufficient to improve the cognitive function of patients with Alzheimer's disease, especially functions relating to language, visuospatial processing, emotion, and cognitive control. Our results were consistent with those of previous studies [14]. In addition, our study also found that the ALFF value in the ORBsupmed of donepezil-treated patients with Alzheimer's disease trended towards normal values, which might be related to the plasticity of the Alzheimer's disease brain [15]. Studies have found that glucose metabolism in the ORBsupmed shows abnormalities with the progression of age [16]. The question of whether donepezil acts by modulating the abnormal metabolism in ORBsupmed warrants further investigation.

Previous studies have found that donepezil enhances the activation of the prefrontal lobes [17] and increases the functional connectivity of the orbitofrontal network; furthermore, it was found to be associated with cognitive improvement after treatment [18]. Studies have also shown that the improvement of frontal lobe function in patients with Alzheimer's disease is associated with the donepezil-induced increase in cerebral blood flow in that region [19]. fMRI has been used to illustrate that donepezil can increase the extent of activation in the ventrolateral prefrontal cortex in patients with mild cognitive impairment [20]. The brain regions that exhibited improvements in the present study were located in the prefrontal lobe, which was consistent with the findings of previous studies. Therefore, it can be speculated that the prefrontal cortex is the major brain region in which donepezil exerts its effects.

In the present study, the baseline ALFF values in the right REC did not differ between patients with Alzheimer's disease and the healthy controls. Following donepezil treatment, the ALFF values in the right REC of patients with Alzheimer's disease decreased significantly. This finding was in line with the results of our previous regional homogeneity study [21]. The REC is located at the junction of the medial and ventral aspects of the frontal lobe [22] and is associated with memory, language and behavior. Knutson *et al.* [23] reported that REC was related to the inhibition of inappropriate behaviors, and injury to the REC could cause behavioral disinhibition and lead to social and emotional impairments, which may result in behaviors such as impulsive behavior and disregard for social conventions. In fact, agitation is a common adverse effect listed on the donepezil label.

The pretreatment ALFF values in the right IFG_{triang} and right ORB_{inf} of patients with Alzheimer's disease were not significantly different from those of the healthy control group. Although the ALFF values increased significantly after treatment in patients with Alzheimer's disease, they were not significantly different from those of healthy controls. This implied that the SNA in the aforementioned normal brain regions increased following treatment, but they were still within normal ranges. Therefore, we speculate that donepezil treats Alzheimer's disease through partial compensation via intact brain regions. However, this compensation is limited and reflects a kind of transient adaptation of Alzheimer's disease. Decompensation occurs once the compensation becomes slower than the functional decline in the brain regions with Alzheimer's disease lesions. A myriad of studies have shown that donepezil significantly improves the MMSE scores of patients in the first few months of Alzheimer's disease treatment, but the scores will subsequently show a downward trend. In other words, donepezil can only delay but not reverse the course of the disease [24].

The main inadequacies and limitations of our study include: (1) small sample size, which is mainly due to the poor compliance of patients with Alzheimer's disease to follow-up schedules. In addition, patients with Alzheimer's disease are susceptible to other diseases, which led to their withdrawal from the study. The inability of patients to maintain a resting state during MRI also rendered some data unusable. (2) For analyses of ALFF, the levels of significance were set at $P < 0.05$ without correction for multiple comparisons because of low statistical power due to the relatively small sample size in the study. (3) We employed the classic 90-region AAL template [25], which is not novel, but the results are relatively stable. (4) Extremely loud environments, claustrophobic situations, fear, stress, and so on, during MRI scan might have affected ALFF. (5) This study is an explorative study and we interpret our findings entirely descriptively.

In summary, we utilized the ALFF analytic metrics of rs-fMRI and found that donepezil could improve cognition-related functions of the frontal lobe. These changes in the brain measured using functional imaging have the potential to serve as biomarkers for assessing the effectiveness of Alzheimer's disease therapies and will be useful for personalized therapy.

Acknowledgments

This work was funded by grants from the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2015KYB073, 2019ZA023, 2020KY509) and the Zhejiang Province Public Welfare Technology Application Research Project (LGF18H090021, LGF19H090017). We thank the technicians of the radiology department of Tongde Hospital of Zhejiang Province for their help in collecting MRI data. We would like to thank Editage (www.editage.com) for English language editing.

Conflicts of interest

There are no conflicts of interest.

References

- 1 Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, *et al.* The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**:270–279.
- 2 Xue SW, Guo Y; Alzheimer's Disease Neuroimaging Initiative. Increased resting-state brain entropy in Alzheimer's disease. *Neuroreport* 2018; **29**:286–290.
- 3 Liu Y, Wang K, Yu C, He Y, Zhou Y, Liang M, *et al.* Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: a review of resting-state fMRI studies. *Neuropsychologia* 2008; **46**:1648–1656.
- 4 Zhao Z, Lu J, Jia X, Chao W, Han Y, Jia J, Li K. Selective changes of resting-state brain oscillations in aMCI: an fMRI study using ALFF. *Biomed Res Int* 2014; **2014**:920902.
- 5 Chao-Gan Y, Yu-Feng Z. DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Front Syst Neurosci* 2010; **4**:13.

- 6 Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 2012; **59**:2142–2154.
- 7 Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007; **38**:95–113.
- 8 Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, *et al.* Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev* 2007; **29**:83–91.
- 9 Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al.* Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002; **15**:273–289.
- 10 Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller HJ, *et al.* The effects of donepezil in Alzheimer's disease - results from a multinational trial. *Dement Geriatr Cogn Disord* 1999; **10**:237–244.
- 11 Zatorre RJ, Evans AC, Meyer E. Neural mechanisms underlying melodic perception and memory for pitch. *J Neurosci* 1994; **14**:1908–1919.
- 12 Northam GB, Adler S, Eschmann KCJ, Chong WK, Cowan FM, Baldeweg T. Developmental conduction aphasia after neonatal stroke. *Ann Neurol* 2018; **83**:664–675.
- 13 Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci* 2007; **8**:393–402.
- 14 Lee JH, Jeong SK, Kim BC, Park KW, Dash A. Donepezil across the spectrum of Alzheimer's disease: dose optimization and clinical relevance. *Acta Neurol Scand* 2015; **131**:259–267.
- 15 Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. *Arch Med Res* 2012; **43**:615–621.
- 16 Jiang J, Sun Y, Zhou H, Li S, Huang Z, Wu P, *et al.* Study of the influence of age in 18F-FDG pet images using a data-driven approach and its evaluation in Alzheimer's disease. *Contrast Media Mol Imaging* 2018; **2018**:3786083.
- 17 Chang WH, Park YH, Ohn SH, Park CH, Lee PK, Kim YH. Neural correlates of donepezil-induced cognitive improvement in patients with right hemisphere stroke: a pilot study. *Neuropsychol Rehabil* 2011; **21**:502–514.
- 18 Griffanti L, Wilcock GK, Voets N, Bonifacio G, Mackay CE, Jenkinson M, Zamboni G. Donepezil enhances frontal functional connectivity in Alzheimer's disease: a Pilot Study. *Dement Geriatr Cogn Dis Extra* 2016; **6**:518–528.
- 19 Hongo J, Nakaaki S, Shinagawa Y, Murata Y, Sato J, Tatsumi H, *et al.* SPECT-identified neuroanatomical predictor of the cognitive effects of donepezil treatment in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* 2008; **26**:556–566.
- 20 Petrella JR, Prince SE, Krishnan S, Husn H, Kelley L, Doraiswamy PM. Effects of donepezil on cortical activation in mild cognitive impairment: a pilot double-blind placebo-controlled trial using functional MR imaging. *AJNR Am J Neuroradiol* 2009; **30**:411–416.
- 21 Cheng J, Yang H, Zhang J. Donepezil's effects on brain functions of patients with Alzheimer disease: a Regional Homogeneity Study based on resting-state functional magnetic resonance imaging. *Clin Neuropharmacol* 2019; **42**:42–48.
- 22 Destrieux C, Terrier LM, Andersson F, Love SA, Cottier JP, Duvernoy H, *et al.* A practical guide for the identification of major sulcogyral structures of the human cortex. *Brain Struct Funct* 2017; **222**:2001–2015.
- 23 Knutson KM, Dal Monte O, Schintu S, Wassermann EM, Raymond V, Grafman J, Krueger F. Areas of brain damage underlying increased reports of behavioral disinhibition. *J Neuropsychiatry Clin Neurosci* 2015; **27**:193–198.
- 24 Mossello E, Tonon E, Caleri V, Tilli S, Cantini C, Cavallini MC, *et al.* Effectiveness and safety of cholinesterase inhibitors in elderly subjects with Alzheimer's disease: a "real world" study. *Arch Gerontol Geriatr Suppl* 2004:297–307.
- 25 Serra L, Mancini M, Cercignani M, Di Domenico C, Spanò B, Giuliotti G, *et al.* Network-based substrate of cognitive reserve in Alzheimer's disease. *J Alzheimers Dis* 2017; **55**:421–430.