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Characterization of brain blood flow and the amplitude of low-frequency fluctuations in major depressive disorder: A multimodal meta-analysis

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ABSTRACT

Background: In healthy subjects, there is an association between amplitude of low-frequency fluctuations (ALFF) and regional cerebral blood flow (rCBF). To date, no published meta-analysis has investigated changes in the regional ALFF in medication-free depressed patients.
Methods: In this study, we aimed to explore whether resting-state rCBF and ALFF changes co-occur in the depressed brain without the potential confound of medication. Using signed differential mapping (SDM), we conducted two meta-analyses, one of rCBF studies and one of ALFF studies, involving medication-free patients with major depressive disorder (MDD). In addition, we conducted a multimodal meta-analysis to identify brain regions that showed abnormalities in both rCBF and ALFF.
Results: A total of 16 studies were included in this series. We identified abnormalities in resting-state rCBF and ALFF in the left insula in medication-free MDD patients compared with healthy controls (HC). In addition, we observed altered resting-state rCBF in the limbic-subcortical-cortical circuit and altered ALFF in the default mode network (DMN) and some motor-related brain regions.
Limitations: The analysis techniques, patient characteristics and clinical variables of the included studies were heterogeneous.
Conclusions: The conjoint alterations in ALFF and rCBF in the left insula may represent core neuropathological changes in medication-free patients with MDD and merit further studying.

1. Introduction

Major depressive disorder (MDD) is characterized by the recurrence of discrete depressive episodes that typically feature symptoms such as depressed mood; anhedonia; poor motivation; impaired psychomotor activity; and reduced sleep, appetite, energy and libido (Fitzgerald et al., 2008). The lifetime prevalence of MDD is high; in the United States, 17% of people reportedly meet the criteria for MDD at least once in their lifetime (Kessler et al., 2005). Despite the development of new treatments for MDD, symptoms have a considerable impact at both the individual and societal level. Understanding the pathophysiology and etiology of MDD remains a challenge for researchers.

Over the past two decades, several functional imaging studies have been conducted to elucidate the brain processes involved in MDD. Recently, resting-state studies, where subjects are asked to rest quietly with their eyes closed during data acquisition, have been used to quantify intrinsic brain activity. Independent of particular tasks, resting-state studies provide a task-free approach that avoids the limitation of performance-related issues (Gusnard and Raichle, 2001). These studies typically use positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) – based techniques, including arterial spin labeling (ASL) and assessment of the amplitude of low-frequency fluctuations (ALFF). PET, SPECT, and ASL can all be used to measure rCBF (Wintermark et al., 2005). ALFF can be used to detect

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Table 1
The demographic and clinical characteristics of the subjects in the functional neuroimaging datasets included in the meta-analyses.

Studies	Modality/analysis	Number (% female)		Mean age (y)		Mean illness duration (months)	HRSD score (17 Items)	Clinical details	Drug status	Quality score (out of 10)
		MDD	HC	MDD	HC					
ALFF Studies										
Guo et al., 2014	ALFF	44(50%)	44(50%)	27.52	29.39	19.61	25.18		Drug-naive	9.5
Liu et al., 2013	ALFF	22(45%)	19(47%)	28.09	24.37	2.95	25.89		Drug-naive	10
Wang et al., 2012	ALFF	18(50%)	18(50%)	34	35	5	25		Drug-naive	10
Wang et al., 2014	ALFF	30(57%)	33(58%)	35.7	31.45	5.48	24.97	Treatment-nonresponsive MDD	Drug-naive	10
Wang et al., 2014	ALFF	26(62%)	33(58%)	32.54	31.45	4	27.5	Treatment-responsive MDD	Drug-naive	10
Yan et al., 2014	ALFF	14(100%)	18(100%)	36	33	4	25.7		Drug-naive or > 2 w washout	10
Zhang et al., 2014	ALFF	32(56%)	35(49%)	20.53	20.97	NA	NA		Drug-naive	9.5
Zhao et al., 2014	ALFF	51(53%)	50(56%)	28	29	NA	NA		Drug-naive	8.5
Liu et al., 2014	ALFF	30(57%)	30(50%)	29.8	30.1	13.3	28.5		Drug-naive	10
rCBF Studies										
Kohn et al., 2007	^{99}mTc -HMPAO SPECT	33(58%)	25(52%)	53	49	NA	NA		> 2 w washout	9.5
Krausz et al., 2007	^{99}mTc -HMPAO SPECT	10(90%)	10(90%)	49.1	49.7	NA	NA	Treatment-sensitive MDD	> 3 w washout	8
Perico et al., 2005	^{99}mTc-ECD SPECT	15(80%)	15(60%)	34.5	33.27	30.6	26.9		> 4 w washout	9.5
Skaf et al., 2002	^{99}mTc-ECD SPECT	9(44%)	12(50%)	41	34	127	35.22		> 4 w washout	8
Vardi et al., 2011	^{99}mTc -HMPAO SPECT	37(57%)	27(58%)	55	50	NA	NA		> 2 w washout	9.5
Drevets et al., 1992	^{15}O-H_2O PET	13(54%)	33(61%)	36	30	NA	NA	MDD with MDD first-degree relatives	> 3 w washout	9.5
Monkul et al., 2012	^{15}O-H_2O PET	20(75%)	21(65%)	37.2	34.8	NA	NA		> 2 w washout	9.5
Lui et al., 2009	ASL	24(33%)	42(36%)	35	37	192	22	Refractory MDD	Drug naive	9.5
Lui et al., 2009	ASL	37(30%)	42(36%)	33	37	24	24	Nonrefractory MDD	Drug naive	9.5

^{15}O-H_2O PET=^{15}O-H_2O positron emission tomography; 17-item HRSD=17-item Hamilton Rating Scale for Depression; ^{99}mTc-ECD SPECT=Technetium-^{99}m ethyl cysteinate dimer single photon emission computed tomography; ^{99}mTc-HMPAO SPECT=Technetium-^{99}m hexamethylpropyleneamine oxime single photon emission computed tomography; ALFF=amplitude of low-frequency fluctuations; ASL=arterial spin labeling; HC=healthy controls; MDD=major depressive disorder; NA=not available; rCBF=regional cerebral blood flow