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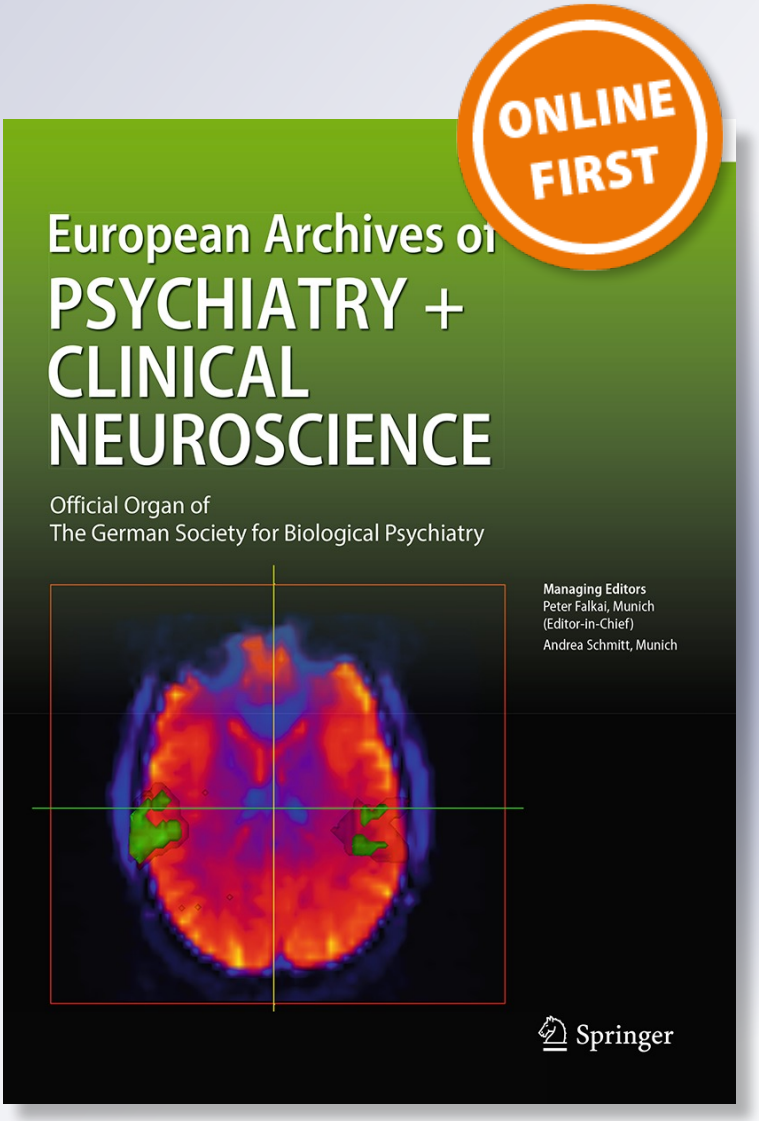

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ORIGINAL PAPER

EEG marker of inhibitory brain activity correlates with resting-state cerebral blood flow in the reward system in major depression

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Abstract Frontal alpha band asymmetry (FAA) is a marker of altered reward processing in major depressive disorder (MDD), associated with reduced approach behavior and withdrawal. However, its association with brain metabolism remains unclear. The aim of this study was to investigate FAA and its correlation with resting-state cerebral blood flow (rCBF). We hypothesized an association of FAA with regional rCBF in brain regions relevant to reward processing and motivated behavior, such as the striatum. We enrolled 20 patients and 19 healthy subjects. FAA scores and rCBF were quantified with the use of EEG and arterial spin labeling. Correlations of the two were evaluated, as well as the association with FAA and psychometric assessments of motivated behavior and anhedonia. Patients showed a left-lateralized pattern of frontal alpha activity and a correlation of FAA lateralization with subscores of Hamilton Depression Rating Scale linked to motivated behavior. An association of rCBF and FAA scores was found in clusters in the dorsolateral prefrontal cortex bilaterally (patients), in the left medial frontal gyrus, in the right caudate head and in the right inferior parietal lobule (whole group). No correlations were found in healthy controls. Higher inhibitory right-lateralized alpha power was associated with lower rCBF values in prefrontal and striatal regions, predominantly in the right hemisphere, which are involved in the processing of motivated behavior and reward. Inhibitory brain activity in the reward system may contribute to some of the motivational problems observed in MDD.

Keywords Major depression · Arterial spin labeling · Reward processing · Approach motivation · EEG · Frontal alpha asymmetry

Introduction

Major depressive disorder (MDD) is a globally highly prevalent disease associated with reduced quality of life, disability and increased medical morbidity [1, 2]. It is characterized by impairments in affective, motor and cognitive symptom dimensions yielding a very heterogeneous phenotype. Neuroimaging studies show structural and functional alterations in multiple brain areas, such as the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), the hippocampus, anterior and posterior cingulate cortex (ACC and PCC) and caudate nucleus [3, 4]. However, the heterogeneity of findings suggests that neurobiological correlates of MDD are still to be fully understood. The electroencephalogram (EEG) allows to directly measure the cerebral activity at the level of populations of neurons, providing a body of multidimensional information about the brain's functional state and neural dynamics with a high temporal resolution. One of the most investigated EEG signatures in MDD is resting frontal alpha bandwidth asymmetry (FAA) [5–7], a pattern of relatively greater left than right resting-state alpha band activity also present in remitted patients [8]. FAA has been associated with withdrawal behavior and reduced approach motivation

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Table 1 Sociodemographic and clinical features for patients and healthy controls

	Patients ($n = 20$)		Healthy subjects ($n = 19$)		Total ($n = 39$)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	43.30	14.03	41.05	13.82	42.21	13.79
Gender	10 female		11 female		21 female	
Smokers	9		4			
Number of episodes	5.85	6.09	–	–	–	–
Duration of illness (years)	10.7	10.29	–	–	–	–
Total HAMD score	25,45	4,95	–	–	–	–
Annual income (CHF)	43.446	32.012	46.452	21.907		
Education years	13.71	2.52	14.21	3.66		

[9, 10]. FAA has moderate heritability and may represent a state-independent risk factor for the disorder [11, 12]. However, some studies challenge this association [13–15], and its potential as a biomarker has still to be confirmed [16, 17]. Indeed, very little is known about the intracerebral correlates of this EEG feature, in particular as measured by magnetic resonance imaging (MRI) techniques. Consequently, the goal of this study is to measure FAA in a cohort of MDD patients and healthy controls and analyze its relationship with a relatively straightforward indicator of baseline brain activity such as resting-state cerebral blood flow (rCBF). This is measured by MRI-based arterial spin labeling (ASL), a direct, noninvasive imaging technique that does not require the use of contrast agents [18]. Given the fact that alpha waves seem to have an inhibitory function on cerebral activity [19], higher EEG alpha power would then hypothetically be associated with lower metabolic rates and cerebral perfusion. Because of the existing body of literature proposing an association between FAA and approach-/avoidance-related behavior [12], we expect to find a correlation between FAA scores and resting-state rCBF in brain regions involved in reward processing and motivated behavior, such as the striatum. Moreover, we hypothesize an association with resting-state rCBF in other cortical areas functionally connected with the striatum and involved in the modulation of behavior as a function of motivation. Finally, an association between FAA and psychometric measures of anhedonia and motivation is expected.

Methods

Subjects

We enrolled 20 inpatients and outpatients with a diagnosis of MDD at the University Hospital of Psychiatry, Bern. Diagnoses were given by experienced psychiatrists using structured interviews (SCID 1 and 2 for DSM-IV-TR). Exclusion criteria included history of substance abuse or dependence (except for nicotine), electroconvulsive therapy or head trauma, as well as bipolar disorder or comorbid personality disorders. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to exclude patients with Parkinsonian symptoms [20]. Hamilton Depression Rating Scale (HAMD) score at screening had to be >18 for the patient to be enrolled [21]. Pre-screening clinical assessment included also the Montgomery–Åsberg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI-II), the Pittsburgh Sleep Quality Index (PSQI) and the Edinburgh Handedness Inventory [22–25]. All patients but one were pharmacologically treated with one or more antidepressants (amitriptyline 25–225 mg, $n = 2$; escitalopram 20 mg, $n = 1$; clomipramine 75 mg, $n = 1$; doxepin 100–200 mg, $n = 2$; mirtazapine 15–45 mg, $n = 6$; sertraline 100–200 mg, $n = 2$; venlafaxine 150–300 mg, $n = 2$; and venlafaxine and mirtazapine combination 150–300 mg/30 mg, $n = 4$). Seven patients received adjunctive agents for augmentation (lithium = 2; lamotrigine $n = 1$, quetiapine $n = 4$), and nine patients received zolpidem 10 mg at night. One of the patients was excluded from the correlation analysis because of the presence of multiple artifacts in the rCBF data. The control group consisted of 19 adults matched for age, gender, education and income, without history of affective disorders or alcohol/drug abuse and without first-degree relatives with affective disorders. All participants were between 21 and 66 years of age. Demographic characteristics are given in Table 1. The two groups did not differ with regard to smoking status. The current sample contains a proportion of subjects with EEG and MRI data from our previous reports [26–29].

EEG data acquisition and processing

Electrophysiological (EEG) data were acquired at the EEG laboratory of the Center for Translational Research, University Hospital of Psychiatry in Bern, with 70 channels. Silver chloride electrodes were positioned in an elastic cap

according to the international 10–20 system. Impedances were kept below 10 kΩ, and the electrode Cz was used as online reference. Data were acquired at a sampling rate of 500 Hz for 6 min, while the subjects were in a relaxed state. After correcting the recordings for eye movement artifacts with the use of independent component analysis [30], the EEG data were referenced using common average reference. Detection and discard of sections containing artifacts were performed by manual inspection. Segments of 2 s length were created from sections recorded with eyes closed, which were subjected to absolute spectral power analysis performing a fast Fourier transform (FFT) and averaged across subjects.

MRI acquisition and analysis

The images were acquired with a 3-Tesla MR scanner (Siemens Magnetom Trio, Erlangen, Germany). High-resolution T1-weighted MR images were obtained using a 3D-modified driven equilibrium Fourier transform (MDEFT) sequence [31]. The optimized acquisition parameters included: 176 sagittal slices with 256 × 224 matrix points with a non-cubic field of view (FOV) of 256 mm × 224 mm, yielding a nominal isotropic resolution of 1 mm^3 (i.e., 1 mm × 1 mm × 1 mm), repetition time (TR) = 7.92 ms, echo time (TE) = 2.48 ms, flip angle = 16°, inversion with symmetric timing (inversion time 910 ms), fat saturation and 12-min total acquisition time.

CBF was then calculated using the noninvasive MRI method pseudocontinuous ASL (pCASL) [32, 33]. The parameters were set as follows: TR = 4000 ms; TE = 18 ms; FOV = 230 × 230 mm^2; matrix size = 128 × 128; 18 axial slices at a distance of 1.0 mm; slice thickness = 6.0 mm; gradient-echo echo-planar readout; ascending order; acquisition time 45 ms per slice; number of measurements $n = 100$; and 7-min total acquisition time.

Structural and perfusion images were processed using SPM8 (Wellcome Trust Center for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing of the perfusion images was conducted using self-written MATLAB toolbox (MATLAB R2014a; The MathWorks, Inc., Natick, MA, USA) and SPM8 [34–36]. ASL images were co-registered to the T1-weighted images, normalized, realigned and re-sliced and smoothed with 8 mm FWHM kernel. From the time series of the ASL signal, the mean regional resting-state cerebral blood (rCBF) flow was calculated voxel-wise.

Statistical analyses

Frontal asymmetry scores were calculated subtracting the natural log-transformed power values of the left hemisphere electrode from the homologous of the right hemisphere (Fp2–Fp1, F4–F3, F8–F7), in lower and upper alpha (respectively, 8–10.5 Hz, 10.5–12.5 Hz). A mixed ANOVA was run on the FAA scores with electrode position and frequency band as within-subject factors and group and sex as between-subject factors. Only significant main effects or interactions wherein direct group or sex comparisons revealed significant differences are reported.

Partial correlations between FAA, HAMD total score and the sum score of items associated with motivated behavior and anhedonia in the HAMD and BDI-II were calculated controlling for age. The HAMD subscale is the sum of the items "work and activities" and "psychomotor retardation," while the BDI subscale is the sum of the items "loss of pleasure," "loss of interest," "loss of energy" and "loss of interest in sex" [37]. Level of significance was set at $p < 0.05$ (two-tailed). Statistical analyses were performed using SPSS (version 22: SPSS Inc, Chicago). Greenhouse–Geisser and Bonferroni corrections were applied where necessary.

Statistical tests on ASL data were performed using SPM8 (Wellcome Trust Center for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm) routines. Effects of categorical and continuous variables on rCBF have been investigated using independent samples t tests and multiple regression analysis, respectively. Age and global mean cerebral blood flow of the participants were included as covariates.

The resulting sets of voxels from each contrast represent a statistical parametric map of the t statistic (SPM-t). We excluded all voxels with <10 ml/min blood flow as well as gray matter values of <0.1 (absolute threshold masking). For statistical analysis, a threshold of $p < 0.001$ (uncorrected) was applied and a minimum cluster size threshold of 17 voxels. This threshold is equivalent to a map-wise false-positive rate of alpha <0.0001 using a Monte Carlo procedure as implemented in the AlphaSim program in the analysis of functional neuroimage software package [38].

Results

When analyzing the FAA scores in a mixed-ANOVA model, a main effect of group was detected [$F(1, 35) = 7.291$, $p = 0.011$], while no main effect of sex was found. Patients had the opposite pattern of lateralization of frontal alpha activity compared to controls, i.e., left-lateralized versus right-lateralized FAA (see Fig. 1). An electrode*group*sex interaction existed [$F(2, 70) = 3.696$, $p = 0.030$], but in post hoc analyses no significant simple two-way interactions of group and sex at the three electrode levels were found.

In the patients group, mean FAA scores across all electrode positions in the alpha band correlated with the HAMD subscore for motivated behavior ($r = -0.640$, $p = 0.003$, Bonferroni corrected, partial correction for age, see Fig. 2) but not with the BDI subscore. No a

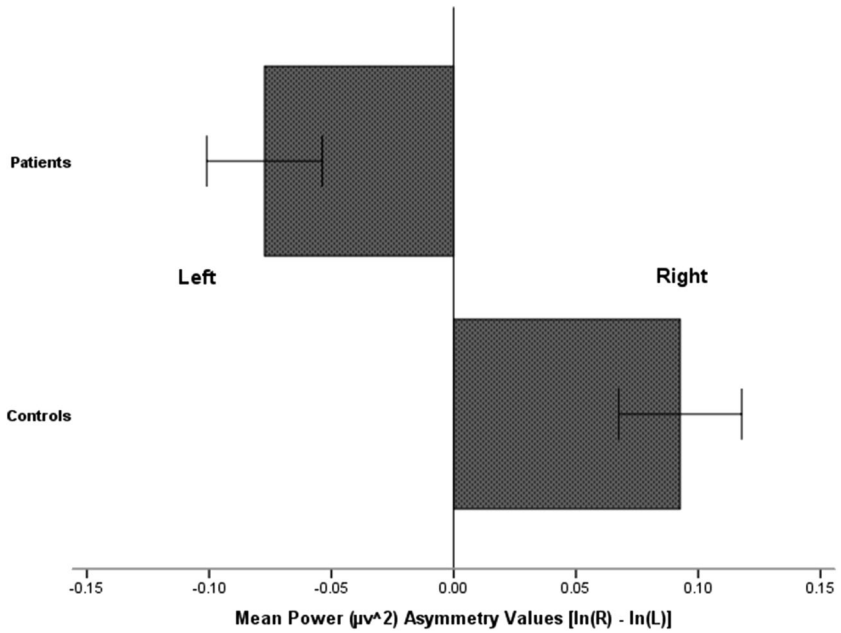

Fig. 1 Mean power (μv^2) [ln(*R*)−ln(*L*)] asymmetry values for all electrodes and alpha subbands in MDD patients and controls, showing the main effect of group. *Error bars*, 1 SEM

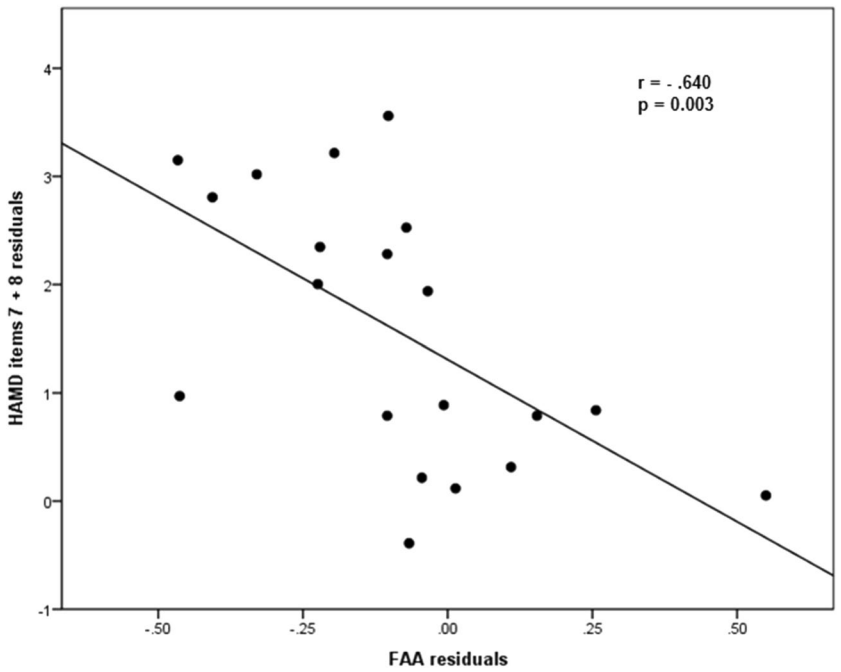

Fig. 2 *Scatterplot* of the residuals obtained when regressing both FAA scores and the HAMD subscore on age (HAMD subscore consists of the sum of the items "work and activities" and "psychomotor retardation"). This illustrates the partial correlation of the first two variables when controlling for age in MDD patients

priori selection between those two subscores was made when investigating the associations, so correction for multiple comparisons was applied. Also, we did not find any significant partial correlation between FAA scores and the HAMD total score in the patients group. No significant correlations at all were found in the group of controls.

No differences in rCBF were found in the group comparison. A significant effect of FAA (mean FAA scores across all electrode positions in the whole alpha range) on resting-state cerebral blood flow was found in patients and in the whole group (patients and controls) but not in controls. In MDD patients, FAA scores correlated negatively with rCBF in right inferior frontal gyrus and in left middle frontal gyrus, i.e., reduced rCBF with stronger right lateralization. Instead, in the whole group, a negative correlation was found between those two variables in the right caudate head/putamen (extending to the ventral striatum, see Figs. 3 and 4), in the right inferior parietal lobule/BA40 and in the left medial frontal gyrus (BA 9) (see Fig. 5). No

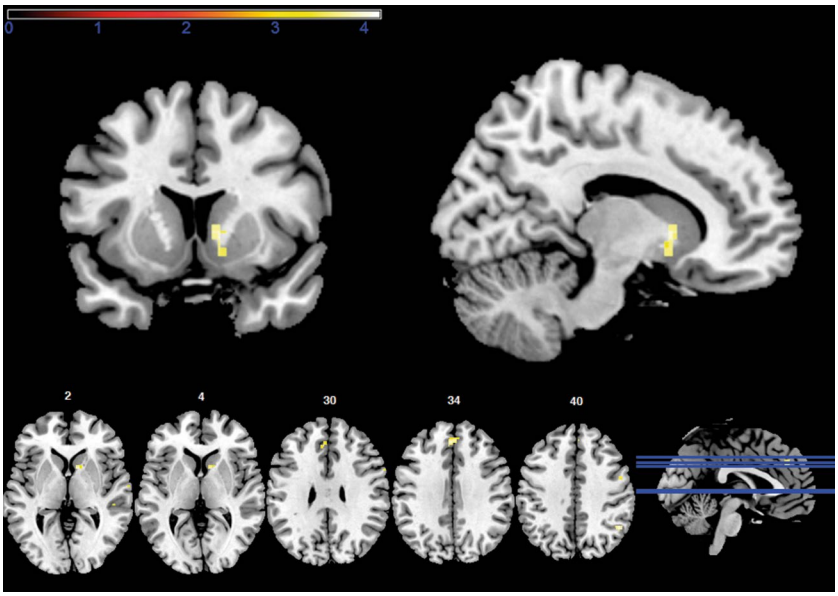

Fig. 3 Effect of FAA on resting-state cerebral blood flow in the whole group. In the *first row*, the striatal cluster is depicted, in the *second row* all clusters are shown. For exact localization and size of the clusters, see Table 3. Above each axial slice, its Talairach z-coordinate is reported (*right* = *right*)

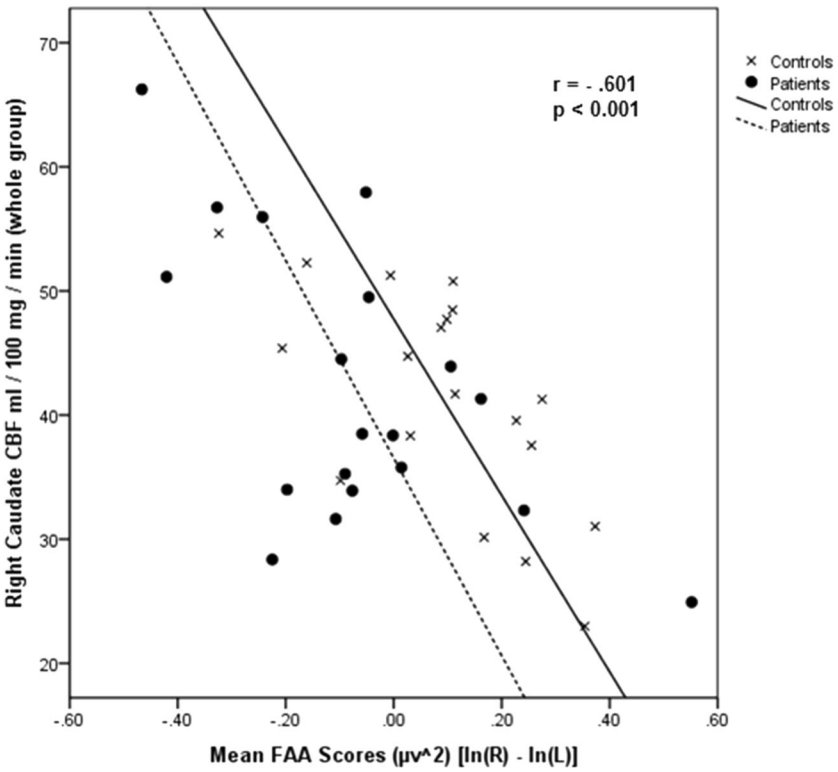

Fig. 4 *Scatterplot* showing the correlation between rCBF and FAA scores and the distribution of MDD patients and controls

areas in which a positive correlation existed were found (see Tables 2 and 3).

Discussion

The objective of this study was to investigate the difference in patterns of lateralization in the frontal alpha band activity (FAA) and the relationship between FAA scores and rCBF in a group of MDD patients and matched healthy subjects. Frontal alpha activity was predominant in the left hemisphere in the patients, while the opposite was true in controls. Moreover, right-lateralized alpha power (higher FAA scores) was correlated with lower rCBF values in prefrontal cortical areas and in the right striatum, both in MDD patients and in the whole group.

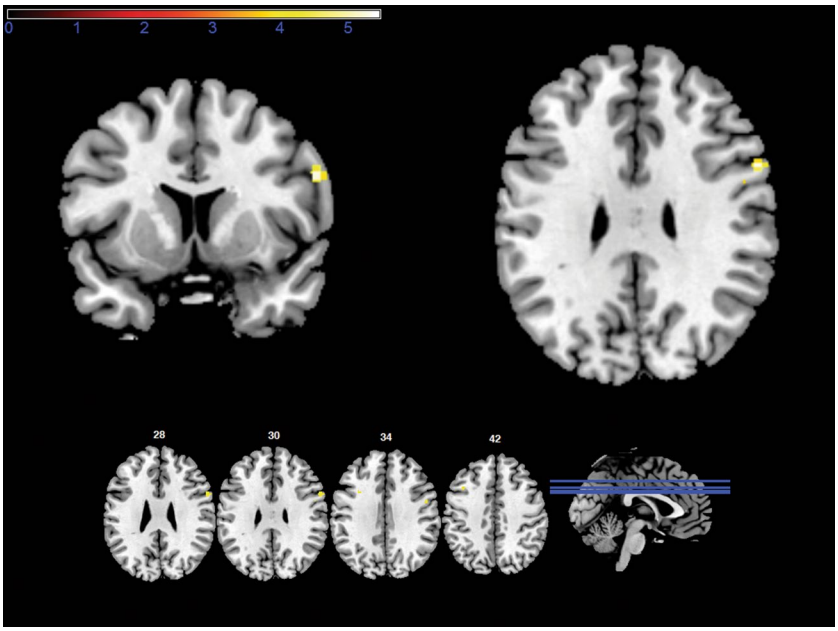

Fig. 5 Effect of FAA on resting-state cerebral blood flow in the patients group. In the *first row*, the cluster in the right inferior frontal gyrus is shown, while in the *second row* all clusters are depicted. For exact localization and size of the clusters, see Table 2. Above each axial slice, its Talairach z-coordinate is reported (*right* = *right*)

Table 2 Areas in which FAA activity scores correlate negatively with rCBF in the patients group ($p < 0.001$ uncorrected, minimum cluster size threshold of 17 voxels)

Brain regions	MNI coordinates			Peak	Cluster size
	x	y	z	T	Voxels
Right inferior frontal gyrus	58	8	30	5.33	22
Left middle frontal gyrus	−38	14	40	4.92	21

Table 3 Areas in which FAA activity scores correlate negatively with rCBF when analyzing the data of patients and controls together ($p < 0.001$ uncorrected, minimum cluster size threshold of 17 voxels)

Brain regions	MNI coordinates			Peak	Cluster size
	x	y	z	T	Voxels
Left medial frontal gyrus/BA 9	−2	38	34	3.95	72
Left medial frontal gyrus	−8	38	48	4.09	20
Right caudate head/putamen	12	10	2	4.02	26
Right inferior parietal lobule/ BA 40	48	−54	40	4.16	23

The result of a left-lateralized pattern of frontal alpha activity in the patients, which differs substantially from the controls, is in line with previous studies, even if some discrepancies exist in the literature [7, 15]. These could be explained by differences in demographic and clinical characteristics, such as psychopathological heterogeneity, sample size, age and gender [6, 13, 14]. The subjects of this study were matched for gender, age, income and education years, probably reducing some of the confounding factors. Furthermore, the previous divergent results could be due to methodological aspects such as differences in EEG montage and reference or in the mathematical calculation of the asymmetry score [14, 39, 40]. The lack of a direct correlation of the FAA scores with measures of symptoms severity such as HAMD scores may seem counterintuitive but is in line with the vast amount of evidence showing an association between frontal alpha band EEG asymmetry and approach/withdrawal-related behavior and affect, more than with depressive symptomatic severity per se [5, 12]. Specifically, right-sided brain activity (as indicated by higher alpha power on the opposite homologous electrode) is thought to be linked to reduced sensitivity to reward and to reduced approach motivation [9, 41, 42], which are behavioral and psychopathological traits that represent core features of the clinical manifestation of depression. This is indeed supported by the negative correlation between FAA and the HAMD sum score of items "work and activities" and "psychomotor retardation." Both of them putatively point at deficits linked to motivated behavior and reward processing, associating more severe impairments with left-lateralized alpha activity. Instead, FAA did not correlate with the BDI subscore. This could be due to the items included in the two subscores, the latter one comprising a larger set of items ("loss of pleasure," "loss of interest," "loss of energy" and "loss of interest in sex") and focusing on a broader construct [37].

No significant differences were found in the group comparison for gray matter resting-state perfusion, while different estimates were reported in a previous study including some of the subjects evaluated here [29]. This could be due

to the different procedures or statistical approaches used to calculate and analyze rCBF. Indeed, when lowering the statistical threshold of our model, we identified some clusters (e.g., right frontal lobe), suggesting the possibility that the analysis of a larger sample may yield more significant results.

When further investigating the neurobiological correlates of frontal alpha asymmetry, we found significant correlations with rCBF in areas of the brain that are part of networks implicated in the modulation of motivated behavior and in other closely intertwined tasks such as cost/benefit decision making and motor planning. This is particularly interesting considering the fact that disturbances of incentive motivation have been frequently reported in depression and other clinical entities, e.g., schizophrenia or bipolar disorder [43]. This would further support the association between frontal alpha asymmetry and the construct of approach behavior and, given the trans-diagnostic nature of those impairments, explain the controversial results obtained in studies specifically designed to elucidate the role of FAA as a biomarker of MDD. The correlation of rCBF and FAA scores in the patients was exclusively inverse and located in the right inferior frontal gyrus and left middle frontal gyrus. Activation of the former seems to reflect risk aversion during risky decision making [44] and is modulated by stimulation of that area [45], while activity in the latter has been shown to play an important role in the reappraisal and cognitive control of emotions [46]. No significant correlations were found in the group of healthy subjects. More interestingly, FAA scores and resting-state CBF in the whole group correlated negatively in the right striatum, in prefrontal cortical regions such as left medial frontal gyrus (BA 9) and inferior parietal lobule (BA 40). The finding of a negative correlation in the striatum, precisely in the head of caudate and in the putamen, is particularly intriguing because of the functional relevance of this area in the processing of reward and motivation [47, 48]. Ventral areas of the striatum are functionally connected to the orbitofrontal cortex, while more dorsal seeds were associated with activity in the dorsolateral prefrontal cortex and other cognitive-related brain regions following a ventrodorsal "affective to cognitive" gradient [49]. The former are thought to be involved in reward evaluation mechanisms, while the latter areas may then represent the link between motivational processes and subsequent planning and adaptive behavior [50, 51].

The current hypothesis about the role of alpha band waves is that they may inhibit or suppress the function of brain areas [19]. The finding of left-lateralized FAA pattern in patients would reflect stronger inhibition and decreased brain activity in the left frontal regions, which is associated with approach behaviors. In turn, higher FAA scores would indicate more inhibitory activity in right frontal areas. This is reflected by the reported inverse correlation between FAA and CBF: The more inhibitory alpha power was lateralized to the right (higher FAA value), the lower was the corresponding rCBF value in prefrontal and striatal regions (see Fig. 4). Indeed, this result fits in the framework of the asymmetry model, in particular when considered in the light of the results of a meta-analysis of 65 fMRI and PET studies, which highlighted a right-sided distribution of withdrawal-related brain activation [52]. More recently, individual bias toward reward was associated with relatively higher D2 receptor binding in regions such as putamen, medial frontal cortex and orbitofrontal cortex of the left hemisphere [53]. In addition, dopamine responsivity in the striatum seemed to have an influence on cost/benefit decision making and behavior [54], increasing proneness to expend effort for larger rewards. Effort-related and approach behaviors are conceptually related and reflect the individual propensity to actively undertake appetitively motivated conducts. Both are putative subdomains of the broader constructs of reward processing and in the previously mentioned studies appear related to left-lateralized striatal dopamine signaling [55, 56].

The negative correlations between rCBF and FAA that we found in the whole group were not limited to striatal seeds but involved also cortical clusters, located in the left medial frontal gyrus and the in right inferior parietal lobule, which have been shown to be functionally connected with the striatum [49, 57–59]. The dorsomedial prefrontal cortex plays a role in the processing of negative emotion [60] in action monitoring and is considered part of the default-mode network (DMN) [61]. The DMN is formed by a group of structures known to show more activity when at rest than when engaging in externally oriented tasks, and has been associated with self-referential processing [62–64]. Furthermore, when comparing MDD patients and healthy controls, Sheline et al. identified a bilateral dorsomedial prefrontal cortex region that exhibited significantly increased functional connectivity with the DMN itself, and other two networks involved in cognitive control and emotional processing. They suggest that increased resting-state connectivity of these nodes through this area may cause an attentional shift toward self-focus and rumination and interfere with task performance and externally oriented activity [65]. Finally, we found a cluster in the right inferior parietal lobule, which corresponds to BA 40. Lesions of this area seem to be responsible for the emergence of apraxia [66]. Notably, neural activity in this region is thought to play a critical role in the process of movement intention and of general subjective feeling of "wanting to move" [67]. In addition, we found that left-lateralized frontal alpha activity and increased power in the lower alpha range over the motor cortex were both correlated with psychomotor retardation in MDD patients, highlighting the importance of

considering motor disturbances in depression in a broader perspective [26].

Taken together, the correlations that we found between rCBF and lateralized alpha activity might be interpreted as the expression of a dysfunction in a group of brain regions that are part of the dopamine networks extending from the striatum to multiple cortical regions. These seem crucial for neural processes involved in motivated, task-oriented decision making and behavior [48, 50, 68]. Impairments in motivational and reward-relevant processing and their subdomains are a hallmark of major depression and other psychiatric disorders as well [43, 69, 70] and correspond to the broad domain of Positive Valence of the Research Domain Criteria (RDoC) matrix [71]. Their disruption (together with those that converge into the Negative Valence domain, such as threat and loss) may underlie some of the main facets of the clinical phenotype of depression [72], behaviorally merging in the unspecific clinical phenomenon of anhedonia [55].

However, this study has several limitations. First, the relatively small sample size of the two cohorts may have limited its power and it may have probably prevented the identification of clusters in other areas in which we were expecting to find an association, such as the orbitofrontal cortex, which plays an important role in motivational and reward-related processing [50]. Moreover, the fact that we found significant effects of FAA on rCBF in the whole group but not in the controls alone could be interpreted as a tendency of the healthy subjects of having less variance in both measures, contributing to the lack of correlation observed. Instead this would become relevant and significant when pooled with the patients' data, aligning them on a spectrum of covariance between EEG and ASL findings. Nevertheless, this finding could also be attributed to the small sample size. Second, all but one patient were pharmacologically treated, and we did not include a non-medicated group. This could be a potential confounder, since antidepressants have been shown to have an impact on rCBF, reducing brain activation in areas with abnormally elevated perfusion in depressed patients, and to decrease EEG alpha power; however, the changes were small and disappeared at higher dosages [73, 74]. Third, we did not directly assess behavioral approach/withdrawal with specific psychometric scales, so our interpretation of the results remains partially hypothetical, although fitting in a solid theoretical framework supported by a large body of evidence [75]. Fourth, the assessments of ASL and EEG were conducted on the same morning but separated by 60–120 min. Therefore, the correlation between neuroimaging methods is valid only if we assume that both resting-state markers (FAA and CBF) would not vary substantially within 2 h.

Conclusions

In summary, our EEG analysis demonstrates a left lateralization of frontal alpha band activity in MDD patients, replicating a finding associated with approach/withdrawal constructs. By investigating the association of this EEG signature with resting-state cerebral blood flow, we detected a pattern of correlations between reduced approach motivation, as measured by frontal alpha asymmetry, and altered perfusion in brain regions (e.g., striatum, frontal cortex) involved in the processing of motivated behavior. Future studies examining in more detail the meaning of these dysfunctions and their mutual relationships may help to construct a more precise and neurobiologically accurate model of those networks and their role in the pathophysiology of MDD.

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Compliance with ethical standards

Ethical standards The study protocol was approved by the local ethics committee and was in accordance with the 1964 Declaration of Helsinki.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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