Research article

EEG cross-frequency correlations as a marker of predisposition to affective disorders

Gennady G. Knyazev [a],[*], Alexander N. Savostyanov [a],[b], Andrey V. Bocharov [a],[b], Lyubomir I. Aftanas [a],[b]

[a] Institute of Physiology and Basic Medicine, Timakova str., 4, Novosibirsk, 630117, Russia
[b] Novosibirsk State University, Pirogova str., 2, Novosibirsk, 630090, Russia

A B S T R A C T

EEG cross-frequency amplitude-amplitude correlation (CF-AAC) has been considered as a potential marker of social anxiety and other affective disturbances. Functional significance of this phenomenon remains unclear, partly because the majority of studies used channel-level analysis, which precluded the spatial localization of observed effects. It is not also clear whether CF-AAC may serve as a marker of specific pathological conditions and specific states, or a more general predisposition to affective disturbances. We used source-level analysis of EEG data obtained in resting conditions in a nonclinical sample and patients with major depressive disorder (MDD) and investigated associations of CF-AAC measures with a broad range of known risk factors for affective disorders, including age, gender, genotype, stress exposure, personality, and self-reported 'neurotic' symptomatology. A consistent pattern of associations showed that all investigated risk factors were associated with an enhancement of CF-AAC in cortical regions associated with emotional and self-referential processing. It could be concluded that CF-AAC is a promising candidate marker of a general predisposition to affective disorders at preclinical stages.

1. Introduction

Affective disorders, such as major depressive disorder (MDD), bipolar disorder, and anxiety disorders have very high prevalence rates all over the world (Eaton et al., 2008). Pathophysiology of these disorders affects motivational, emotional, and cognitive processes, which may depend on different genetic and environmental factors. The study of neural correlates of these processes may help to understand the etiology of affective disorders and their early detection and prevention. Functional magnetic resonance imaging (fMRT) is currently the leading tool in this field, but it has serious limitations, such as low temporal resolution and indirect relation to neuronal events (e.g., Debener et al., 2006). Electroencephalography (EEG), which is a more accessible and cost-effective method than fMRI, has excellent temporal resolution and a more direct relation to neuronal events. In fact, recent findings support the view that oscillations of electrical activity in the brain in traditional EEG frequency bands may provide a mechanism for task-related functional integration of distant brain areas (Buzsaki and Draguhn, 2004; Engel et al., 2013). Recently,

one EEG phenomenon, namely, cross-frequency amplitude-amplitude correlation between slow (delta and theta) and fast (alpha and beta) oscillations (sfCF-AAC), has particularly attracted attention of researchers in the field of neural correlates of affective states (Harrewijn et al., 2016, 2017; 2018; Knyazev, 2011; Knyazev and Slobodskaya, 2003; Knyazev et al., 2005, 2006; Miskovic and Schmidt, 2012; Miskovic et al., 2010, 2011a; 2011b; Putman, 2011; Putman et al., 2012; Rutherford et al., 2018; Schutter and van Honk, 2004, 2005; Schutter et al., 2006; Velikova et al., 2010). In particular, sfCF-AAC between frontal delta and beta oscillations has been suggested as a candidate genetic trait marker of social anxiety (Harrewijn et al., 2017, 2018).

There is much evidence that oscillations in traditional EEG frequency bands are somehow related to different physiological and psychological processes (da Silva, 2013; Nunez, 2000). Delta and theta oscillations are associated with motivational and emotional processes, whereas higher frequency oscillations are related to attention and inhibitory control (Aftanas et al., 2001, 2004; Guntekin and Basar, 2010; Klimesch, 1999; Knyazev, 2007, 2012; 2013; Jensen et al., 2014; Spaak et al., 2012).

However, different physiological and psychological processes must interact with each other and must be integrated in order to produce a consistent holistic behavior (Deco et al., 2015). In EEG domain, such integration could be observed in a form of interactions between different frequency oscillations, which has been termed cross-frequency coupling and has recently attracted much attention of researchers (Cole and Voytek, 2017; Helfrich et al., 2016; Palva and Palva, 2018). It should be kept in mind, however, that this term could be used for different kinds of interactions between different frequency oscillations such as, for instance, as phase-phase and phase-amplitude coupling (PAC) (Canolty and Knight, 2010; Jensen and Colgin, 2007), or amplitude-amplitude correlations in the within- or between-subject domain (see Schutter and Knyazev, 2012 for a review). These latter correlations may not reflect the current operations in the brain, which evidently occur only in the within-subject domain and at faster temporal scales, but they could be related to some slower processes, such as moods or traits. It has been empirically shown that in terms of behavioral correlates, sfCF-AAC and PAC are quite different phenomena (Poppelaars et al., 2018).

In spite of considerable differences between the studies in applied sfCF-AAC measures, experimental conditions, and composition of samples, the general pattern of results seems to support the view that enhanced sfCF-AAC is a marker of aversive affective states. It has been observed in subjects with social anxiety (Harrewijn et al., 2016, 2018; Miskovic et al., 2010, 2011b), high behavioral inhibition (Knyazev and Slobodskaya, 2003), high salivary cortisol level (Schutter and van Honk, 2005), and during anxious anticipation (Harrewijn et al., 2018; Knyazev, 2011; Knyazev et al., 2005, 2006). Functional significance of this marker is not clear. One drawback of existing studies is that they mostly used channel-level analysis. Source-level analysis may show where in the brain this phenomenon is most frequently observed and thus help to elucidate its provisional functional significance. Given the known functional correlates of slow and fast EEG oscillations, it could be speculated that enhanced sfCF-AAC reflects efforts to suppress enhanced negative emotions. If this interpretation is correct, it could be expected that enhanced sfCF-AAC could be most reliably observed in pathological groups and/or in relevant states. In non-clinical samples and in resting condition, it should correlate with traits predisposing to affective disorders and with subjective level of environmental stress. The aim of this study was to test these predictions.

We used source-level analysis of sfCF-AAC in a large non-clinical sample and in MDD patients. sfCF-AAC measures were compared in healthy controls and in MDD patients, which, to the best of our knowledge, has not been done previously. In the non-clinical sample, we investigated the association of sfCF-AAC measures with a dimensional self-report measure of psychopathological symptoms. Besides, we investigated the association of sfCF-AAC measures with known risk factors for affective disorders, including age, gender, personality, exposure to psychosocial stress, and genetic factors.

Internalizing problems peak in mid-to-late adolescence and tend to decrease from adolescence to adulthood (Petersen et al., 2018; Sheidow et al., 2008). Therefore, in young adult samples, a negative correlation with age could be expected for a presumptive marker of affective disturbances. It should be also higher in females than in males, because female gender is a risk factor for a variety of affective disorders including anxiety disorders, major depression, dysthymia, atypical depression, and seasonal winter depression (McLean and Anderson, 2009; Piccinelli and Wilkinson, 2000). Personality traits of neuroticism and introversion have also been recognized as risk factors for affective disorders (Clark et al., 1994; Farmer et al., 2002; Jylhä and Isometsä, 2006; Naragon-Gainey et al., 2009). Much evidence shows that exposure to psychosocial stress is associated with the onset of affective disorders (Kessler, 1997; Siegrist, 2008; Tennant, 2002). The effect of stress on appearance of psychopathological symptoms is particularly pronounced in vulnerable individuals with a genetic predisposition (Heim and Binder, 2012); and polymorphism of the serotonin transporter gene (5-HTTLPR) is one of the most investigated genetic factors of vulnerability to stress, anxiety, and

depression (e.g., Gressier et al., 2016). It should be noted that whereas earlier studies have found a significant effect of 5-HTTLPR on the development of major depression disorder (MDD) (e.g., Caspi et al., 2003), many later studies failed to replicate this finding (e.g., Clarke et al., 2010; Munafò et al., 2009; Risch et al., 2009; Sharpley et al., 2014). Much more consistent results, however, were obtained in neuroimaging studies of emotional reactivity. Thus, many studies have linked 5-HTTLPR S allele carrying with a heightened amygdala response to negative emotional stimuli (Hariri et al., 2002; Munafò et al., 2009; Schinka et al., 2004; Sen et al., 2004; Thomason et al., 2010) and a stronger influence of long-term stress exposure on the structure and activity of brain regions involved in emotion regulation (Canli et al., 2006; Selvaraj et al., 2011). In this study, we used 5-HTTLPR as a marker of heightened emotional reactivity and sensitivity to stress.

We hypothesized that sfCF-AAC would be higher in MDD patients than in controls. In the non-clinical sample, they would negatively correlate with age, should be higher in individuals who are homozygous on the short 5-HTTLPR allele (S/S), than in heterozygous individuals (S/L) and individuals who are homozygous on the long 5-HTTLPR allele (L/L). Moreover, sfCF-AAC should be higher in females than in males and should correlate positively with self-report measures of affective psychopathological symptoms, introversion, neuroticism, and psychosocial stress.

2. Methods

2.1. Participants

Non-clinical sample (sample 1) included 115 adults (41 men; mean age = 25.5, SD = 9.2). They were mostly graduate and postgraduate students and staff members of Novosibirsk State University. Clinical sample (sample 2) included 30 patients (10 men; mean age = 34.6, SD = 10.1) with an acute MDD episode. To compare MDD patients with healthy participants, 54 age-, sex-, and education-matched controls (23 men; mean age = 32.0, SD = 10.1) were selected from the non-clinical sample (sample 3). There were no significant differences in age and gender distribution between patients and controls (both p > 0.1). Mental health of patients and controls was assessed by a psychiatrist using an unstructured interview based on the ICD-10 criteria (WHO, 1992). The severity of depression in patients was additionally assessed using the Structured Clinical Interview for DSM-IV and DSM-V. Exclusion criteria for all participants were somatic diseases, seizures, and substance abuse or dependence. Additional exclusion criteria for healthy participants were any mental health problems. Additional exclusion criteria for patients were atypical forms of depression and any additional psychiatric disorder. Institute of Physiology and Basic Medicine ethical committee has approved the study. Written informed consent was obtained from all participants. Demographic and clinical characteristics of the samples 2 and 3 are presented in Table 1.

2.2. Procedure

Participants were seated in a soundproof and dimly illuminated room for EEG registration. Resting state EEG was recorded during six 1-min episodes (3 with eyes closed and 3 with eyes open) alternating sequentially. Eyes closed and eyes open conditions were combined in the subsequent analysis. After EEG registration, participants completed a set of questionnaires.

2.3. Psychometric instruments

Given that existing evidence does not allow linking sfCF-AAC measures with specific affective disorders, we chose Self-Reporting Questionnaire (SRQ-20) for measuring mental health problems (Beusenberg and Orley, 1994). This questionnaire assesses symptoms of depression, anxiety, and somatic problems. The Cronbach's alpha was 0.91.

Table 1. Demographic and clinical characteristics of samples 2 and 3.

Variables (mean ± SD)	MDD (n = 30)	HC (n = 54)	p value[a]
Gender (M: F)	10 : 20	23 : 31	0.28
Age (years)	34.6 ± 10.1	31.8 ± 10.1	0.22
Education level (years)	13.2 ± 2.1	12.9 ± 3.4	0.55
First episode: recurrent	16 : 14	-	
Severity[b]	6.4 ± 0.9	-	
Duration of illness (years)	6.2 ± 8.6	-	
Number of depressive episodes	3.7 ± 5.1	-	
Antidepressant free: users	20 : 10	-	
Acutely depressed	30	-	
HAMD	17.2 ± 4.9	-	
BDI-II	30.9 ± 10.9	7.1 ± 7.4	<0.001

MDD - major depressions disorder; HC - healthy controls; SD - standard deviation; HAMD - Hamilton Depression Rating Scale; BDI-II – Beck Depression Inventory II.

[a] p value for the two-sample t-test of MDD and HC.

[b] number of DSM-IV MDD criteria met (on basis of DSM-IV interview ranging from 0 to 9).

Psychosocial stress level was measured by the Holmes and Rahe's Social Readjustment Rating Scale (SRRS) (Holmes and Rahe, 1967). This scale describes a series of life events and asks whether the respondent had experienced any of them in the previous two years. Personality was assessed using the IPIP 50 Big-Five Factor Markers (Goldberg, 1992; Knyazev et al., 2010). In this sample, Cronbach's alphas were 0.85 for extraversion, 0.74 for agreeableness, 0.77 for conscientiousness, 0.87 for neuroticism, and 0.80 for openness.

2.4. Genotyping

DNA was extracted from buccal cells. Polymerase chain reaction was used to detect the S and L alleles in the DNA samples using 50-ggcgttgccgctctgaattgc-30 and 50-gagggactg agctggacaacccac-30 primers (Lesch et al., 1996). Size of the amplicon was 529 bp for L allele and 489 bp for S allele. To determine the LA/LG polymorphism, the products of amplification were digested for 3 h with MspI endonuclease. The sizes of the products of the digestion of the LA allele were 340, 127 and 62 bp, whereas for the LG allele they were 174, 166, 127 and 62 bp. The LG allele was grouped with S alleles and was labeled as S.

2.5. EEG recording and preprocessing

The Quik-Cap128 NSL with 118 electrodes mounted according to the extended International 10–10 system was used for EEG registration. The electrooculogram was also recorded. 'Neuroscan (USA)' amplifiers with 0.1–100 Hz analog band-pass filter were used for signal multiplication. Sampling rate was set at 1000 Hz. FASTRAK digitizer (Polhemus) was used to measure the position of each electrode and three fiduciary points (nasion and two preauricular points). The fronto-central electrode was used as ground and vertex as the reference. Electrode impedances were below 5 kilo-ohms. Independent component analysis was used for artifact rejection. The number of rejected components was not significantly different in patients and controls and in participants with different genotypes and did not correlate with psychometric variables. Data were down-sampled to 125 Hz and re-referenced to average reference.

2.6. EEG data reduction

2.6.1. Filtering

EEG data were frequency filtered into the delta, alpha, and beta bands using a Butterworth filter and the Matlab's filtfilt function. To account for individual differences in bands' boundaries (Klimesch, 1999), we used individual alpha peak frequency as the anchor point (Doppelmayr et al.,

1998). Frequency of the maximal alpha power was determined at parietal and occipital channels in the eyes closed condition. Then, EEG spectrum data in the eyes open condition were subtracted from the data in the eyes closed condition and the frequency at which alpha power was most attenuated was determined. If the two peak frequencies did not differ more than 0.5 Hz, the result of the second method was used as individual alpha peak frequency (IAF). Otherwise, IAF was determined by visual inspection of the EEG spectrum (Lansbergen et al., 2011). The bandwidth for delta, alpha, and beta were defined as 0.5–0.4*IAF, 0.8*IAF–1.2*IAF, and 1.2*IAF–25, respectively.

2.6.2. Beamforming

Coregistration and forward model computation were performed using the SPM-12 software (http://www.fil.ion.ucl.ac.uk/spm/). For forward modeling, we used the boundary element head model (Fuchs et al., 2001). The cortical mesh with 5124 vertices was obtained from a template MNI brain. Individual electrode positions of each dataset were co-registered with the template brain using the three fiduciary points. According to SPM-12 manual, "combining the template head model with the individual head-shape, as measured based on individual electrode positions, results in a quite precise head model" (Ashburner et al., 2014, p. 122). SPM-12 toolbox for beamforming (DAiSS, https://code.google.com/p/spm-beamforming-toolbox/) was used to project the data into source space using the linearly constrained minimum variance beamforming (Van Veen et al., 1997). Covariance matrices were generated independently for each frequency band and regularized using a lambda value of 0.05% of the signal variance (Litvak et al., 2010). Time-series of each source was projected along the dipole direction that explains most variance (Ahlfors et al., 2010). Hilbert transform was applied to each source time course to derive the 'analytic signal'. The absolute value of the analytic signal, which is equivalent to the amplitude envelope of oscillatory power, was averaged over 1 s-long windows. Then, in each participant separately, correlations were calculated for each source between the down-sampled Hilbert envelopes in delta and alpha (DA-AAC) and delta and beta (DB-AAC) bands. Correlations were Fisher Z-transformed and mean-centered for each participant separately in order to remove individual variability in the overall strength of correlations. The obtained correlation maps were converted into the NIFTI format, smoothed spatially (FWHM 8 mm) and used in the subsequent second-level statistical analyses.

2.7. Statistical analysis

In this study we used nonparametric statistical methods. Statistical nonparametric mapping toolbox (SnPM13) (Nichols and Holmes, 2002) was used for the group-level random-effects analyses. The cluster-defining primary threshold was set at p = 0.001 and cluster extent threshold corresponded to p = 0.05 (FWE-corrected). Additional correction for the number of analyses was performed using the false discovery rate (FDR) method (Benjamini and Hochberg, 1995). FDR correction was calculated using the collection of p values obtained in all analyses and the q level of 0.05. The obtained corrected p value threshold was 0.037. Only effects that passed this threshold are reported. All regression analyses were performed controlling for participant's age and gender.

3. Results

In the non-clinical sample (sample 1), independent samples T-tests showed that females had higher scores on agreeableness (t = 4.2, p < 0.001) and neuroticism (t = 3.3, p = 0.001) than males. There were no gender differences in age, SRQ scores, and other personality variables. There were 39 L/L, 57 L/S, and 19 S/S 5-HTTLPR allele carriers. The distribution of males and females among different genotype groups was not significantly different (p > 0.05). One-way ANOVA showed no significant effects of genotype on personality and SRQ scores (all p > 0.1). SRQ scores correlated negatively with conscientiousness (r = -0.25, p =

0.007) and positively with neuroticism (r = 0.52, p < 0.001). Besides, age correlated positively with conscientiousness (r = 0.30, p = 0.001) and negatively with neuroticism (r = -0.19, p = 0.043). Comparison of MDD and control groups (samples 2 and 3) showed that they did not differ in age, gender, and education (all p > 0.1). Most of patients were antidepressant free (Table 1). A series of one-sample T-tests (on non-centered sfCF-AAC maps) showed that for all sfCF-AAC measures, only positive coefficients were significant across the entire cortex.

The effect of participant's age on sfCF-AAC measures was analyzed using the mass-univariate linear regression method. The design matrix included a column of ones to model the intercept, participant's age as a covariate of interest, and participant's gender as a covariate of no interest. Both DA-AAC and DB-AAC correlated negatively with participants' age in the retrosplenial posterior cingulate cortex (PCC, Table 2). Because age also negatively correlated with neuroticism and positively with conscientiousness, these analyses were repeated controlling for neuroticism and conscientiousness scores. Although the size of significant clusters diminished, the effect of age remained significant in both cases.

Independent samples T-tests were used to compare sfCF-AAC measures in males and females. These analyses showed that both DA-AAC and DB-AAC were higher in females than in males in the right postcentral gyrus and left parahippocampal gyrus, respectively (Table 2). The opposite effect (i.e., males > females) was not significant.

To test the hypothesis that sfCF-AAC measures should be higher in S/S than in L/S and in L/S than in L/L carriers we used a linear regression model. The design matrix included a column of ones, the genotype group membership, and participant's age and gender as covariates of no interest. L/L genotype carriers were coded by -1, L/S by 0, and S/S by 1. The hypothesis was confirmed for DA-AAC (Table 2). As Figure 1 shows, DA-AAC measures are higher in S allele carriers in the left insula. The opposite effect was not significant.

Regression of SRRS scores controlling for age and gender yielded positive associations with DA-AACs in the left inferior parietal lobule, left postcentral gyrus, and left middle frontal gyrus and with DB-AACs in the left middle frontal gyrus and precentral gyrus (Table 2). These areas are marked by red blobs at Figure 2.

Effects of neuroticism and extraversion controlling for age and gender were also analyzed using the linear regression method. Neuroticism correlated positively with DA-AAC in the anterior cingulate cortex (ACC), whereas extraversion correlated negatively with the same measure in the medial prefrontal cortex (MPFC) (Table 2, Figure 3).

SRQ-20 scores were positively associated with DA-AAC in the medial frontal and cingulate gyri (Table 2, Figure 4). The opposite effect was not significant.

Independent samples T-tests showed that sfCF-AACs were higher in patients than in controls in the left middle temporal gyrus and were higher in controls than in patients in the right post- and pre-central gyri, left middle frontal gyrus, right temporoparietal junction (rTPJ), and right insula (Table 2, Figure 5).

4. Discussion

In this study, our main premise is that CF-AAC measures in general, and sfCF-AAC in particular, reflect some kind of coordination or integration of different computational modes and, ultimately, different psychological processes in the brain. Given the known functional correlates of slow and fast EEG oscillations, it seems reasonable to suggest that sfCF-AACs reflect some kind of interaction between motivational/emotional and regulatory/cognitive domains. Augmentation of these interactions may occur in stressful situations or in individuals with increased sensitivity to stress. Correspondingly, we expected that sfCF-AAC measures should correlate positively with the subjective level of environmental stress and with traits associated with higher stress sensitivity. The

Table 2. All significant effects (controlling for sex and age).

DA-AAC				DB-AAC			
Location	x y z	size	p	Location	x y z	size	p
Age (-)							
PCC	-13 -41 2	66	.007	PCC	-13 -44 7	24	.004
Females > males							
PostC	21 -32 65	20	.024	PhG	-15 -42 5	7	.029
5_HTTLPR (S/S > L/S > L/L)							
Insula	-37 -4 -3	45	.006				
Stress (+)							
IPL	-39 -38 45	902	.005	MiFG	-17 -4 65	51	.032
PostC	-59 -16 31	160	.027	PreC	-33 -4 55	56	.037
MiFG	-41 4 39	99	.020				
Neuroticism (+)							
ACC	-7 20 33	186	.009				
Extraversion (-)							
MFG	-7 48 35	45	.016				
SRQ (+)							
MFG	-9 12 47	144	.012				
CG	-11 -8 47	58	.012				
MDD patients > controls							
				MTG	-57 -5 -25	61	.006
MDD patients < controls							
PreC	43 0 47	425	.001	Insula	35 -32 19	52	.002
MiFG	-25 4 45	114	.004	PostC	61 -6 25	54	.007
rTPJ	49 -56 35	33	.01				

x y z - MNI coordinates of the peak of the cluster; size – cluster size in voxels. p – FWE-corrected cluster p. Effect sign is shown in parentheses. ACC – anterior cingulate cortex; CG - cingulate gyrus; IPL - inferior parietal lobule; MFG – medial frontal gyrus; MiFG – middle frontal gyrus; MTG - middle temporal gyrus; PCC – posterior cingulate cortex; PhG - parahippocampal gyrus; PostC - postcentral gyrus; PreC - precentral gyrus; rTPJ – right temporoparietal junction.
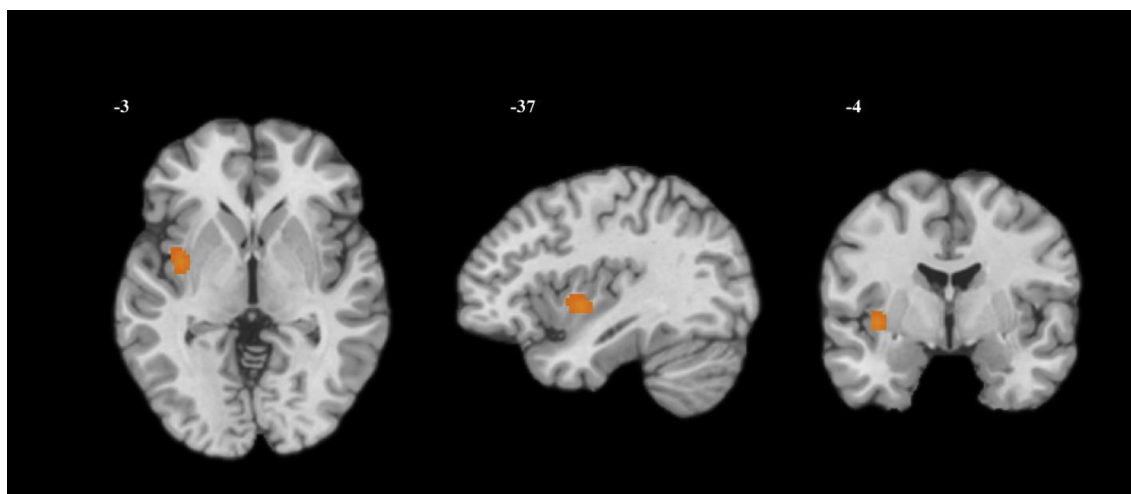
Figure 1. Effect of 5-HTTLPR on DA-AAC (S/S > L/S > L/L) on DA-AAC (n = 115). Warm tints show clusters where DA-AAC measures are higher in S allele carriers.
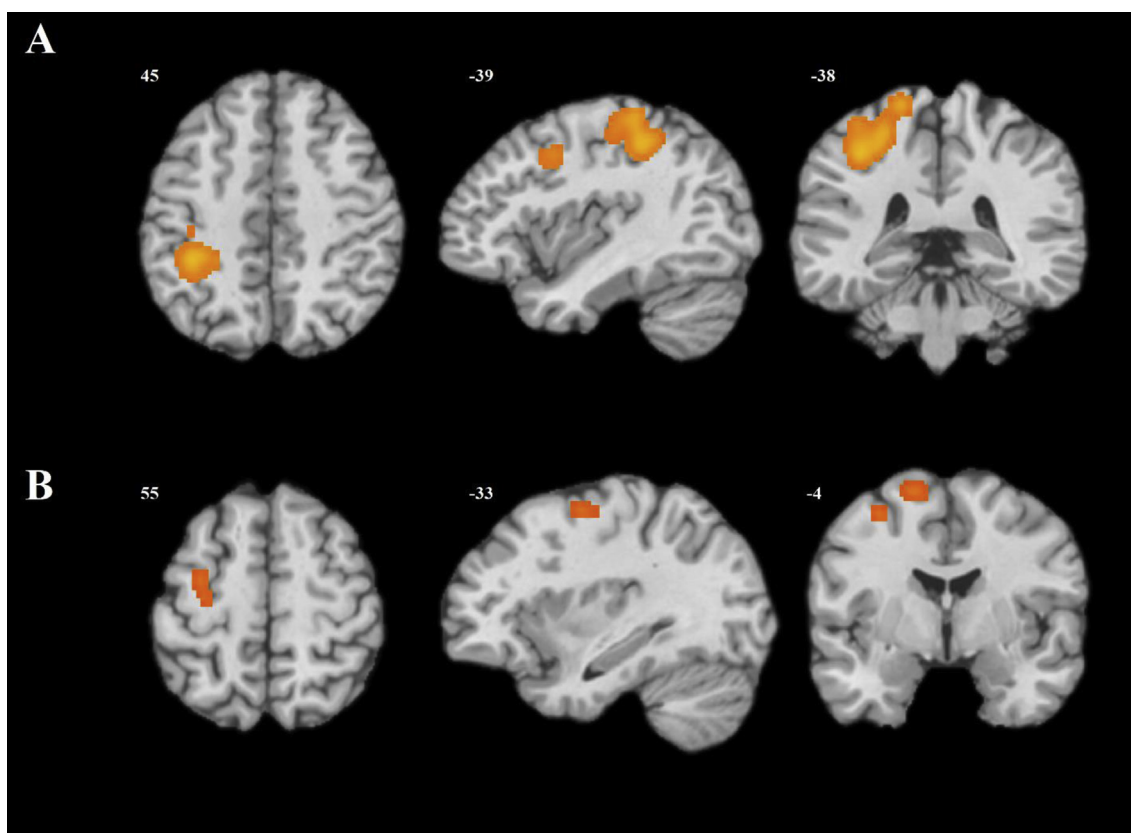

Figure 2. Regression of stress (SRRS scores) on DA-AAC (A) and DB-AAC (B) maps (n = 115). Warm tints show clusters where sfCF-AAC measures correlate positively with SRRS scores.

general pattern of results confirms these expectations. Indeed, sfCF-AACs correlated positively with psychosocial stress level. Moreover, they were higher in females than in males, in younger than in older participants, in 5-HTTLPR S allele carriers than in non-carriers, in introverts than in extraverts, in emotionally unstable than in emotionally stable individuals, and in individuals reporting higher levels of 'neurotic' symptoms than in individuals with low level of these symptoms. An additional argument for the hypothesis linking sfCF-AAC measures with emotion regulation may be the localization of observed effects in brain regions that are related to these processes.

Our results show that 5-HTTLPR S allele carriers demonstrate a heightened DA-AAC in the insula, which is implicated in emotion processing (Gasquoine, 2014; Sepede et al., 2015) and is the key region of the salience network involved in detecting and filtering motivationally salient stimuli (Dosenbach et al., 2007; Seeley et al., 2007). Noteworthy, neuroticism, the key personality trait associated with heightened sensitivity to stress and a predisposition to affective disorders (Clark et al., 1994; Farmer et al., 2002; Jylhä and Isometsä, 2006) showed a positive association with TA-AAC in the ACC, another key region of the salience network (Dosenbach et al., 2007; Seeley et al., 2007).
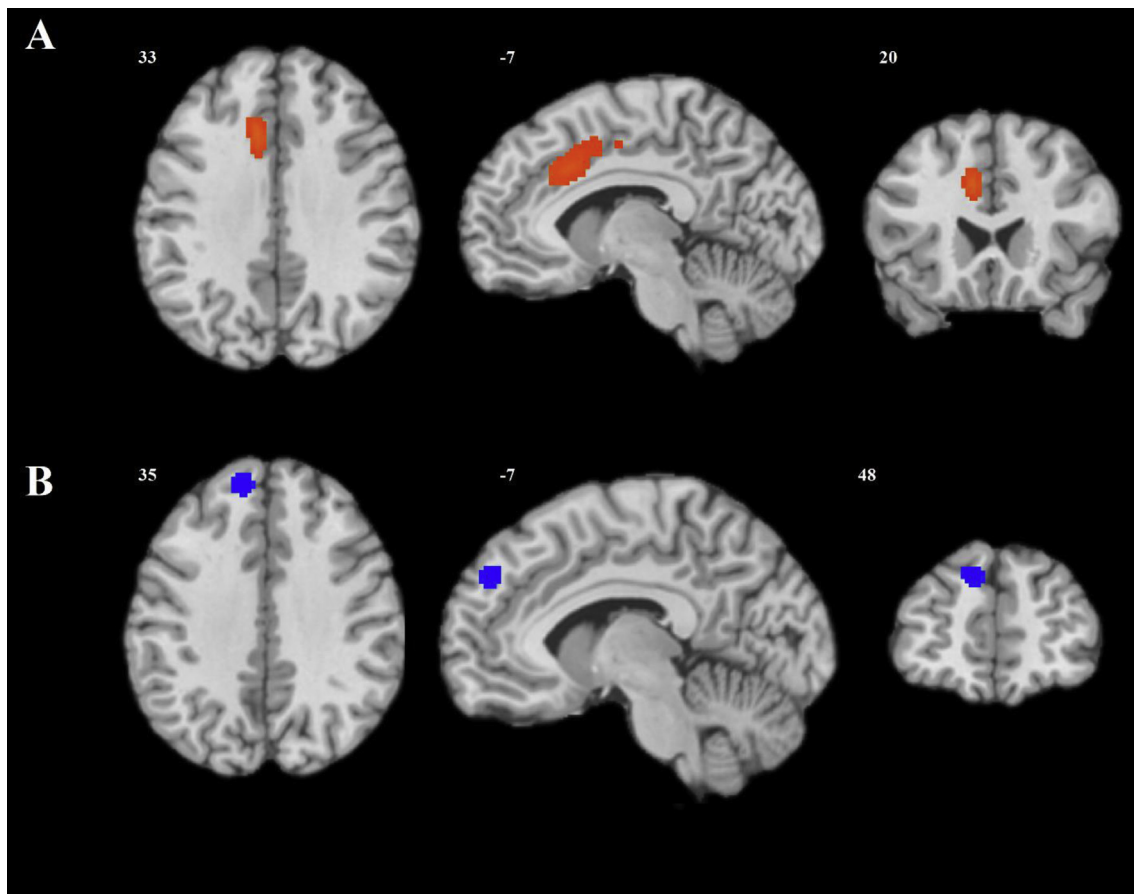
Figure 3. Effect of personality on DA-AAC (n = 115). A – effect of neuroticism; B – effect of extraversion. Warm tints show clusters where sfCF-AAC measures correlate positively and cool tints show clusters where they correlate negatively with respective personality scales.
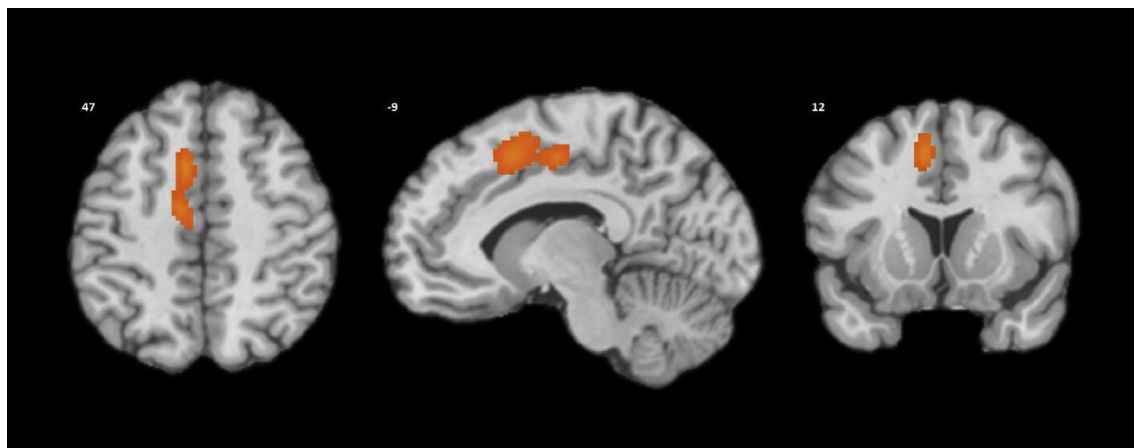

Figure 4. Regression of SRQ scores on sfCF-AAC maps (n = 115). Warm tints show clusters where sfCF-AAC measures correlate positively with SRQ scores.

Moreover, introversion and self-reported neurotic symptoms were associated with heightened TA-AAC in the MPFC, which along with the ACC is involved in the processing and regulation of emotion (Etkin et al., 2011) and is one of the key regions of the default mode network (DMN) implicated in self-referential processing (Davey et al., 2016; Raichle et al., 2001). The most pronounced effect of stress was also revealed in one of the major DMN hubs – the left inferior parietal lobule (IPL), which is a part of the core self-reference network (Davey et al., 2016); the effect of age showed up in the major DMN hub, namely, the PCC (Davey et al., 2016). This fits well with notion linking the DMN

with processing of self-related emotional information (Qin and Northoff, 2011). Besides IPL, stress was associated with increased sfCF-AAC values in the motor and somatosensory cortex and in the middle frontal gyrus associated with executive control functions (Japee et al., 2015; Talati and Hirsch, 2005), which is in line with the idea that emotional stress increases the need for the control of movement and attention (Pereira et al., 2010; Tsai et al., 2018). Besides, recent evidence shows that somatosensory cortex could be implicated in the perception of emotional expressions and the discrimination among emotion categories (Kragel and LaBar, 2016). It is interesting that females show higher
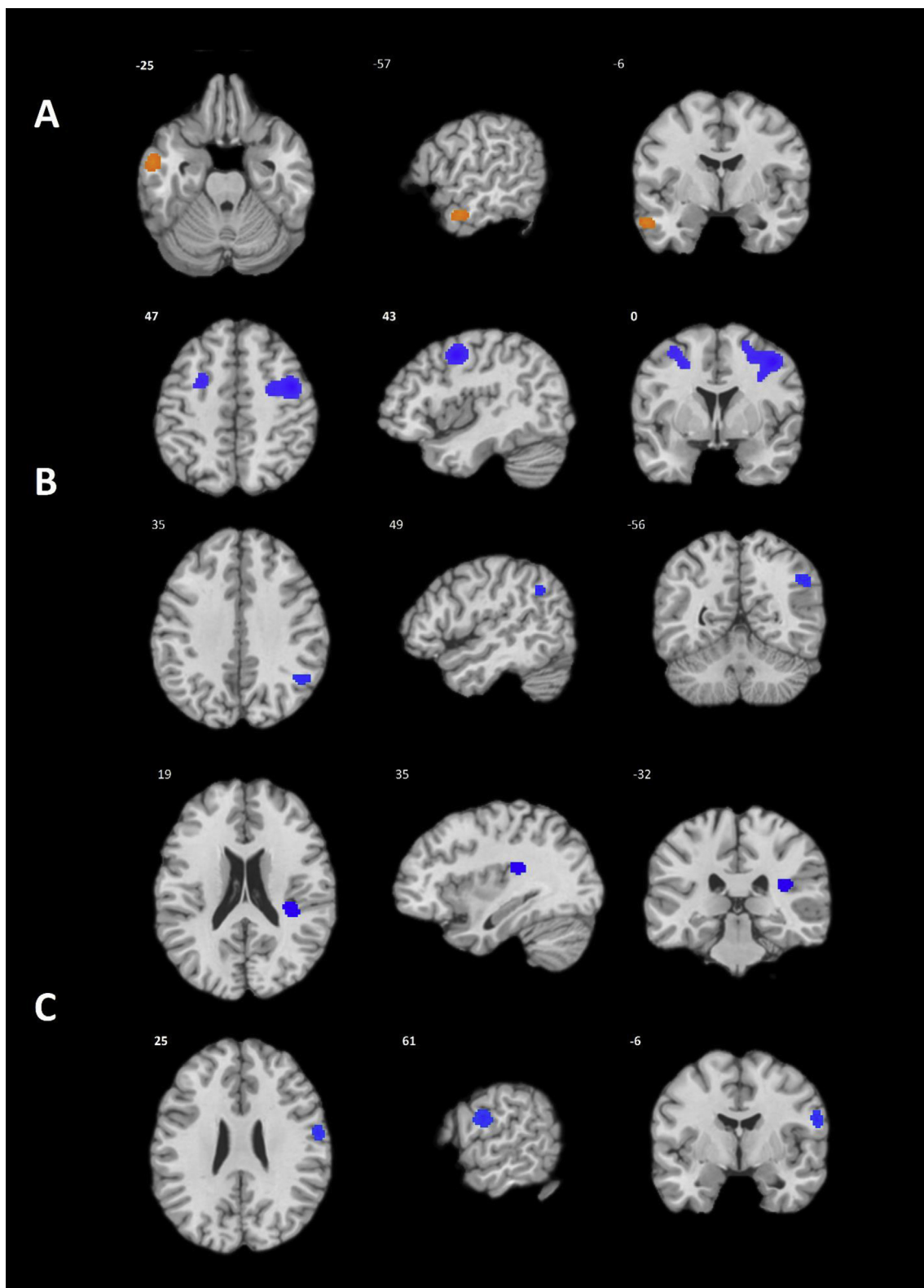
Figure 5. Results of independent samples T-tests comparing sfCF-AAC measures in MDD patients and controls. A - DA-AAC (patients > controls); B - DA-AAC (patients < controls); C - DB-AAC (patients < controls). Warm tints show clusters where sfCF-AAC measures are higher in patients and cool tints show clusters where they are higher in controls.

DA-ACC values in the right somatosensory cortex than males. They also show higher DB-ACC values in the left parahippocampal gyrus whose involvement in emotion processing is well established (Gosselin et al., 2006; Smith et al., 2004; Van den Stock et al., 2014). Thus, overall, both the direction and the localization of observed in the nonclinical sample effects corroborate the idea that sfCF-AAC measures could be treated as a marker of predisposition to affective disturbances and heightened stress sensitivity.

A more complex pattern of results was observed in MDD patients. As compared to controls, they showed higher sfCF-AACs in some regions (anterior part of the left middle temporal gyrus), but lower in others (rTPJ, insula, post- and pre-central gyri). In order to understand this pattern of results, it is important to recognize that although stress reactivity is a well-established major risk factor for developing depressive disorders (Heim and Binder, 2012), the state of clinical depression is associated with diminished reactivity to all emotional stimuli (Anderson et al., 2011; Scheuerecker et al., 2010; van Wingen et al., 2011), as well as with diminished motor activity (Volkers et al., 2003). This allows to understand the observed in MDD patients diminished sfCF-AACs in insula implicated in emotion processing (Gasquoine, 2014; Sepede et al., 2015) and in the motor and somatosensory cortex. Another feature of depressive states is a diminished quantity and quality of social interactions (Nezlek et al., 1994; Weightman et al., 2014). This may explain the diminished sfCF-AACs in the rTPJ, which is involved in the processing of goals, intentions, and beliefs of others (Saxe, 2006; Van Overwalle and Baetens, 2009) and is considered the key region of the social brain (Carter and Huettel, 2013). Simultaneously, MDD patients showed an increase of sfCF-AAC in the anterior part of the left middle temporal gyrus, which is associated with semantic processing (Smith et al., 2004; Xu et al., 2015) and is frequently included in the extended DMN because it participates in the processing of self-related emotional information (Buckner et al., 2008). This finding is similar to Kumari et al. (2003) finding, who showed that cognitive generation of affect in MDD patients is accompanied by a decreased response in the ACC, MPFC, and hippocampus and an increased response in the left middle temporal gyrus (Kumari et al., 2003). It has been suggested that self-focused rumination is one of the major features of depression-related cognitive states (Hamilton et al., 2011). These states are characterized by a decreased activity and connectivity of so-called task-positive networks (TPN), such as the salience network, and a 'dominance' of the DMN over the TPN (Hamilton et al., 2013; Menon, 2001). Since ruminative states are commonly accompanied by an increase in the retrieval of emotionally relevant semantic information, this may involve the left middle temporal gyrus (Xu et al., 2015). Interestingly, a significantly greater DMN connectivity to the left middle temporal gyrus has been observed in participants with a family history of MDD than in controls with no such history (Norbury et al., 2011) and the magnitude of MDD symptoms has been found to be correlated with the strength of connections between the precuneus and the left middle temporal gyrus (Crowther et al., 2015). An enhanced activation in the left middle temporal gyrus was observed by Cooney et al. (2010) in depressed patients compared to healthy controls during the ruminative versus abstract condition. Thus, it appears that the observed in MDD patients increase of sfCF-AAC values in the left middle temporal gyrus and their decrease in rTPJ, insula, and motor/somatosensory cortex may reflect the peculiar to depression ruminative state with increased self-focus and diminished activity and attention to the environment.

Another important question is whether DA-AAC and DB-AAC are distinct phenomena in terms of their psychological correlates. DB-AAC is more popular and is more frequently used in the literature, whereas DA-AAC is largely ignored. Data presented in Table 2 show that the direction of associations is similar for both measures and DA-AAC actually shows more significant effects, at least with factors that have been investigated in this study.

This study has several limitations. Firstly, we used a limited set of psychometric instruments and it did not include a measure of social anxiety, which most frequently has been investigated in previous studies (e.g., Harrewijn et al., 2016, 2017, 2018; Miskovic et al., 2010, 2011a, 2011b). It could be expected that DB-AAC would show stronger association with such a measure. Another limitation is that EEG data were collected in a resting state. Some studies show that sfCF-AACs increase in situations modelling anxiety (e.g., Harrewijn et al., 2018; Knyazev et al., 2006). However, our results show that sfCF-AACs show a consistent pattern of associations with relevant factors even in a resting state. A limitation of our source localization method is that individual structural MRIs were not available and a template head model was used instead. However, since position of each electrode was measured, the individual head shape and size were taken into account. Such approach results in a quite precise head model and is presently recommended as the method of choice for EEG data (Ashburner et al., 2014, p. 122). Nevertheless, one should always keep in mind that EEG data based spatial information should be interpreted with caution due to the inherent ill-posedness of EEG inverse problem.

In conclusion, the phenomenon of sfCF-AAC has attracted much attention of researchers in the field of neural correlates of affective states as a potential trait marker of affective disturbances. Many studies have investigated this phenomenon both in clinical and nonclinical samples in resting condition and in experimental situations using different measures calculated either in the within- or between-subject domains. In spite of considerable accumulated evidence, the functional significance of this phenomenon remains unclear, partly because the overwhelming majority of published studies used channel-level analysis, which precluded the spatial localization of observed effects. Another drawback of existing evidence is that it does not allow to conclude whether sfCF-AACs may serve as a marker of specific pathological conditions (e.g., social anxiety) and/or specific states (e.g., the state of anxious anticipation), or it allow to reveal a more general predisposition to affective disturbances even in nonclinical samples and in resting conditions. Here we used source-level analysis of EEG data obtained in resting condition in nonclinical and clinical samples and investigated associations of two different sfCF-AAC measures with a broad range of known risk factors for affective disorders, including age, gender, genotype, stress exposure, personality, and self-reported 'neurotic' symptomatology. A consistent pattern of associations has been revealed showing that all investigated risk factors are associated with an enhancement of sfCF-AACs in cortical regions associated with emotional and self-referential processing, as well as in motor and sensorimotor cortical areas. Changes revealed in MDD patients relative to controls are consistent with the framework describing depression as a ruminative state with diminished motor activity and attention to the environment. These results allow considering sfCF-AAC as a promising candidate marker of predisposition to affective disorders even at preclinical stages.

Declarations

Author contribution statement

Gennady G. Knyazev: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Alexander N. Savostyanov, Andrey V. Bocharov: Performed the experiments; Analyzed and interpreted the data.

Lyubomir I. Aftanas: Contributed reagents, materials, analysis tools or data.

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