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Default Mode Network alterations in individuals with high-trait-anxiety: an EEG functional connectivity study

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Short running title: DMN connectivity and Trait-Anxiety

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Abstract

Background: Although several researches investigated Default Mode Network (DMN) alterations in individuals with anxiety disorders, up to now no studies have investigated DMN functional connectivity in non-clinical individuals with high-trait-anxiety using quantitative electroencephalography (EEG). Here, the main aim was to extend previous findings investigating the association between trait anxiety and DMN EEG functional connectivity.

Methods: Twenty-three individuals with high-trait-anxiety and twenty-four controls were enrolled. EEG was recorded during 5 min of resting state (RS). EEG analyses were conducted by means of the exact Low-Resolution Electromagnetic Tomography software (eLORETA).

Results: Compared to controls, individuals with high-trait-anxiety showed a decrease of theta connectivity between right medial prefrontal cortex (mPFC) and right posterior cingulate/retrosplenial cortex. A decrease of beta connectivity was also observed between right mPFC and right anterior cingulate cortex. Furthermore, DMN functional connectivity strength was negatively related with STAI-T total score (i.e., lower connectivity was associated with higher trait anxiety), even when controlling for potential confounding variables (i.e., sex, age, and general psychopathology).

Limitations: Small sample size makes it difficult to draw definitive conclusions. Furthermore, we did not assess state variation of anxiety, which make our interpretation specific to trait anxiety.

Conclusions: Taken together, our results suggest that high-trait anxiety individuals fail to synchronize DMN during RS, reflecting a possible top-down cognitive control deficit. These results may help in the understanding of the individual differences in functional brain networks associated with trait anxiety, a crucial aim in the prevention and in the early etiology understanding of clinical anxiety and related sequelae.

Key Words: Default Mode Network; EEG Functional connectivity; eLORETA; Psychopathology; Trait anxiety

Introduction

"Trait anxiety" refers to a relatively stable individual difference characterized by harm avoidance behavior (e.g., worrying), difficulty to relax and tendency to perceive a wide range of environmental events as dangerous and threatening (Spielberger and Sydeman, 1994; Sylvers et al., 2011). High anxiety trait is considered a crucial vulnerability factor for psychopathology, especially for mood and anxiety disorders (Weger and Sandi, 2018).

From a neurophysiological and neurobiological point of view, several studies have shown that individuals with high-trait-anxiety are characterized by different brain structural and functional alterations (Sylvers et al., 2011). For example, it has been reported that high trait anxiety is associated with reduced thickness in the medial prefrontal cortex (mPFC) (Hu and Dolcos, 2017; Kuhn et al., 2011; Spampinato et al., 2009), precuneus (Miskovich et al., 2016) and restrosplenial cortex (Spampinato et al., 2009). Furthermore, functional magnetic resonance imaging (fMRI) investigations in individuals with high-trait-anxiety revealed abnormal activations of both cortical (e.g., PFC) and subcortical regions (e.g., amygdala) during emotional (Comte et al., 2015; Dickie and Armony, 2008; Etkin et al., 2004; Stein et al., 2007) and cognitive tasks (Basten et al., 2011, 2012; Bishop, 2009; Zhang et al., 2016) as well as during resting state (RS) condition (Baur et al., 2013; Kim et al., 2011; Modi et al., 2015; Tian et al., 2016; Yin et al., 2016). Finally, quantitative electroencephalographic (qEEG) studies (i.e., EEG coherence and EEG power spectra) showed that high trait anxiety is associated with several neurophysiological abnormalities, such as increased cortical arousals and EEG desynchronization, during emotional stimuli processing (Aftanas et al., 1996; Aftanas and Pavlov, 2005; Aftanas et al., 2003; Knyazev et al., 2008), anxiogenic situations (Knyazev et al., 2005; Knyazev et al., 2006b), cognitive tasks (Knyazev et al., 2006a; Savostyanov et al., 2009) and RS condition (Aftanas and Pavlov, 2005; Knyazev et al., 2004; Pavlenko et al., 2009; Putman, 2011).

An important advance in neuroscience research, reflecting the modern concept of the brain as a highly integrated and dynamic system, is the assessment of functional connectivity in brain networks (i.e., a set of areas with activity that tends to increase or decrease in synchrony), in both healthy and neuropsychiatric patients (Sylvester et al., 2012).

The Default Mode Network (DMN) is one of the functional brain networks that most frequently shows abnormalities associated with psychopathology (Broyd et al., 2009; Whitfield-Gabrieli and Ford, 2012). It is thought to be involved in several higher-order integrative mental functions, including self-consciousness, self-processing and emotion regulation (Schilbach et al., 2008; Sylvester et al., 2012). The DMN is predominantly detected during the RS condition, when individuals are not actively engaged in goal-directed or attention-demanding tasks (Mak et al., 2017; Neuner et al., 2014). It has been conceptualized as a distributed network characterized by high neural activity and temporal synchrony among different brain regions, such as anterior cingulate cortex (ACC), posterior cingulate/retrosplenial cortex (PCC/Rsp), mPFC, temporoparietal junction (TPJ) (Buckner et al., 2008; Mak et al., 2017; Thatcher et al., 2014; Whitfield-Gabrieli and Ford, 2012).

Although several researches investigated DMN alterations in patients with anxiety disorders (Kim and Yoon, 2018; Peterson et al., 2014), up to now, only few studies selectively focused on non-clinical individuals with high trait anxiety. Modi et al. (2015), in a fMRI study, reported that, compared to individuals with low-trait-anxiety participants, individuals with high-trait-anxiety showed reduced functional connectivity in several regions of the DMN, such as right PCC, left temporal and parietal lobe. Similarly, more recently, Zidda et al., (2018) documented that connectivity strength of right amygdala and hippocampus with the DMN were negatively related to trait anxiety (i.e., individuals with high-trait-anxiety show reduced connectivity).

To the best of our knowledge, no studies have investigated DMN functional connectivity in individuals with high-trait-anxiety using qEEG, a suitable tool for the assessment of this network (Neuner et al., 2014; Thatcher et al., 2014) offering an important source of information for

researchers and clinicians (e.g. qEEG data directly relate to dynamic postsynaptic activity in the cerebral cortex with a high temporal resolution) (Canuet et al., 2011). Therefore, the main aim of the present study was to extend these previous findings investigating the association between trait anxiety and DMN EEG functional connectivity, using the exact Low Resolution Electromagnetic Tomography software (eLORETA), a validated tool for localizing sources of brain electric activity (Pascual-Marqui et al., 1994).

Materials and Methods

Participants

Participants were recruited through advertisements posted in the university. The enrollment lasted from October 2017 to June 2018. Inclusion criteria were: age ≥ 18 years, both genders, negative anamnesis for psychiatric and/or neurologic diseases; right handedness assessed through the Italian version of Edinburgh Handedness Inventory (EHI; Oldfield, 1971; Salmaso and Longoni, 1985); assumption central nervous system active drugs (i.e., anticonvulsants, antipsychotics, opioids, antidepressants and anti-anxiety, illegal drugs) in the four weeks prior to study entry. A checklist with dichotomous items was used to assess inclusion criteria as well as socio-demographic data. Furthermore, in order to identify the presence, past and/or present, of mood disorders and other psychiatric conditions, all participants underwent a clinical interviewer performed by a trained researcher, with screening questions, specifically prepared for this study, and based on the last edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Participants with positive screening for any mental disorders were then excluded. Fifty-eight respondents were assessed for eligibility. Forty-seven participants (twelve men and thirty-five women, mean age: 22.55 ± 2.30 years) fulfilled the inclusion criteria and were enrolled in the present research (see Figure 1 for participants flow diagram). Study participants contributed voluntarily (i.e., they did not receive payment or academic credit) after providing informed consent

that was performed according to the Helsinki declaration standards. The study was approved by the European University's ethics review board.

Questionnaires

After providing the written consent, all participants were administered the Trait subscale of the Spielberger's State-Trait Anxiety Inventory (STAI-T; Spielberger et al., 1983), and the Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983).

The STAI-T (Spielberger et al., 1983) is a 20 item self-report commonly used to assess trait anxiety (Elwood et al., 2012; Julian, 2011). Respondents are asked to rate each item on a 4-point Likert-type scale, ranging from 1 (almost never) to 4 (almost always). The total score ranges from 20 to 80, with higher scores indicating greater trait anxiety. The STAI-T is widely used in both clinical sample and general population and it is characterized by good psychometric properties (Elwood et al., 2012). In the present study we used the Italian version of the STAI-T (Pedrabissi and Santinello, 1989). The Cronbach's α in the present sample was 0.92 for the STAI-T total score.

The BSI (Derogatis and Melisaratos, 1983) is the short version of the Symptom Checklist-90R (Derogatis, 1977) and it is composed by 53 items on 5-point Likert scale (0-4) assessing nine primary symptom dimensions (e.g., somatization and obsessive-compulsive symptoms, depressive symptoms). The BSI also provides a global severity index (GSI) which is designed to measure overall psychological distress. Higher scores indicate more self-reported symptoms. In the present study, the GSI was used as a measure of general psychopathology. The BSI is widely used in clinical research and it is characterized by good psychometric properties (Derogatis and Savitz, 1999). In the present study, a previously validated Italian version of the scale (De Leo et al., 1993) was used and the Cronbach's alpha in the present sample was 0.91 for the GSI.

EEG recordings

RS recordings were performed in an EEG Laboratory. Participants were comfortably sitting with their eyes closed, in a quiet, semi-darkened silent room; the EEG recording lasted at least 5 minutes. Participants were asked to refrain from drinking alcohol and caffeine immediately before their EEG recordings (i.e., at least 4 hours).

EEG was recorded by means of a Micromed System Plus digital EEGraph (Micromed© S.p.A., Mogliano Veneto, TV, Italy). EEG recordings included 31 standard scalp leads, positioned according to the 10-20 system (recording sites: Fp1, AF3, F3, FC1, C3, CP1, P3, PO3, O1, F7, FC5, T3, CP5, T5, Fz, Cz, Pz, Fp2, AF4, F4, FC2, C4, CP2, P4, PO4, O2, F8, FC6, T4, CP6, T6), Electro-oculography and the Electrocardiography. The reference electrodes were placed on the linked mastoids. Impedances were kept below 5KΩ before starting the recording and checked again at the end of the experimental recording. Sampling frequency was 256 Hz; A/D conversion was made at 16 bit; pre-amplifiers amplitude range was ±3200 μV and low-frequency pre-filters were set at 0.15 Hz. The following band-pass filters were used: high frequency filters (HFF) = 0.2 Hz; low frequency filters (LFF) = 128 Hz. In the present study the following frequency bands was considered: delta (0.5–4 Hz); theta (4.5–7.5 Hz); alpha (8–12.5 Hz); beta (13–30 Hz); gamma (30.5–60 Hz).

Visual artifact rejection (e.g., cap adjustment, body movement) was firstly performed on the raw EEG trace (Imperatori et al., 2014a; Imperatori et al., 2013; Imperatori et al., 2014b). At least 180 seconds of artifact-free EEG recording (not necessarily consecutive) were selected for each participant. These segments were removed, and then independent component analysis (ICA) was applied to EEG recordings to identify and remove non-cerebral artifacts, such as eye movements, cardiac pulses and muscular activations before data analysis (see Kam et al., 2013; Vecchio et al., 2015 for details). Specifically, we removed 1.97 ± 1.04 components from total 31 ICA components in this study. Although it has been showed that ICA correction may affect EEG coherence measures (Castellanos and Makarov, 2006), correcting artifacts using this method is widely used in EEG phase synchronization studies (Kam et al., 2013; Li et al., 2017; Moazami-Goudarzi et al., 2008), and

several investigation also reported no significant modifications of EEG coherence data after ICA correction (Kam et al., 2013; Li et al., 2017; Moazami-Goudarzi et al., 2008).

All EEG analysis were performed by means of the eLORETA software, a validated tool for localizing the sources of electric activity in the brain (Pascual-Marqui et al., 1994), characterized by a well documented localization agreement with different multi-modal imaging techniques (Thatcher et al., 2014). Furthermore, the eLORETA is considered a suitable tool to investigate DMN network activity and connectivity (Neuner et al., 2014; Thatcher et al., 2014) *"*assessing changes in the synaptic synchrony of millions of neurons connected at varying time delays and frequencies*"* (Thatcher et al., 2014). Indeed, compared to other neuroimaging technique, such as fMRI, EEG time-series data directly relate to dynamic postsynaptic activity in the cerebral cortex with higher temporal resolution (Canuet et al., 2011), offering a potentially valuable complementary source of information for researchers and clinicians in a relatively cheap manner (Todder et al., 2012).

Connectivity analysis

The connectivity analysis was performed by the computation of lagged phase synchronization (Pascual-Marqui, 2007; Pascual-Marqui et al., 2011), which is widely used in clinical neurophysiology studies (Canuet et al., 2012; Pagani et al., 2012), because, compared to other connectivity measures, it is characterized by several advantages (e.g. it is minimally affected by low spatial resolution) (Pascual-Marqui et al., 2011; Stam et al., 2007). The lagged phase synchronization evaluates "the similarity of two time series by means of the phases of the analyzed signal" (Olbrich et al., 2014), whit values ranging from 0 (i.e., no synchronization), to 1 (i.e., the highest possible synchronization).

According to previous qEEG studies (Farina et al., 2018; Imperatori et al., 2017; Imperatori et al., 2016; Thatcher et al., 2014), in order to evaluate the connectivity in the DMN, 12 Regions of Interest (ROIs) were defined (Table 1). The eLORETA computed the lagged phase synchronization

values between all the "ROIs" (i.e., 144 connections). The eLORETA also computed the source reconstruction (Pascual-Marqui et al., 1994, 1995). As recommended in previous studies (Canuet et al., 2011; Pascual-Marqui et al., 2011), the 'single nearest voxel' option (i.e., each ROI consisted of a single voxel, the closest to each seed) was chosen.

Statistical analysis

The distribution of STAI-T score in the present sample was tested for normality (Shapiro–Wilk test, $p > 0.05$). Successively, according to previous neuroimaging (Etkin et al., 2004; Grachev and Apkarian, 2000; Modi et al., 2015; Modi et al., 2014) and EEG studies on trait anxiety (Aftanas and Pavlov, 2005; Aftanas et al., 2003; Savostyanov et al., 2009; Takacs et al., 2015), participants were divided into two groups based on the STAI-T median value.

Therefore, participants with their trait anxiety scores above and below the median constituted the high-anxiety (STAI-T+) and low-anxiety (STAI-T–) groups, respectively.

EEG connectivity data were compared between STAI-T+ and STAI-T– participants for each frequency band. The comparisons were performed using the statistical non-parametric mapping (SnPM) methodology supplied by the eLORETA software, which is based on Fisher's permutation (Nichols and Holmes, 2002). Correction of significance for multiple testing was computed for the comparisons between STAI-T+ and STAI-T– groups for each frequency band using the non-parametric randomization procedure, available in the eLORETA program package (Holmes et al., 1996; Nichols and Holmes, 2002). For all comparisons, the eLORETA software provides experimental values of T, corresponding to a significance of $p < 0.01$ and $p < 0.05$ (Friston et al., 1991).

Chi-squared test and Kolmogorov-Smirnov Z test were used to analyze differences between groups, respectively, for dichotomous and dimensional measures. Spearman's *rho* correlation coefficients were reported as measures of associations among the STAI-T, GSI, and any significant

EEG connectivity data. Due the strong relationship between STAI-T and psychopathology (Weger and Sandi, 2018), and between DMN EEG connectivity and general psychopathology (Farina et al., 2018), the GSI was also included as control variable in a partial correlation (r_p) analyses. Age and gender were also considered as covariates. Furthermore, another partial correlation analyses has been performed considering depressive and anxiety items of the STAI-T and controlling for age, gender and depressive subscale (DEP) of the BSI (see **supplementary data**). Indeed, although the STAI-T total score is widely used as a measure of general trait anxiety (Julian, 2011), factor analytic studies suggest that a bi-factor model (Balsamo et al., 2013; Bieling et al., 1998), consisting of depression (STAI-T-D) and anxiety (STAI-T-ANX), best fits the data. Two-way chi-squared test, Kolmogorov-Smirnov Z test and correlation analyses were performed using IBM SPSS Statistics for Windows, version 19.0. The use of nonparametric tests was chosen because several variables (i.e., GSI) were not normally distributed (Shapiro–Wilk test, $p< 0.05$).

Results

EEG recordings suitable for the analysis were obtained for all participants. Visual evaluation of the EEG recordings performed by a trained neurophysiologist showed no relevant modifications of the background rhythm frequency, focal abnormalities or epileptic discharges, evidence of drowsiness or sleep during the recordings.

Following scoring of the STAI-T, participants were categorized as high or low trait anxious using a median split which occurred at 45 (23 STAI-T+ participants, and 24 STAI-T– participants). Compared to STAI-T– participants, STAI-T+ participants reported higher mean scores on the GSI. No significant differences were observed for socio-demographic data. Differences between groups are reported in Table 2.

Connectivity results

In the comparison between STAI-T+ and STAI-T– individuals the thresholds for significance, corrected for multiple testing, were T= ±3.58 corresponding to $p< 0.05$, and T= ±4.01, corresponding to $p< 0.01$. Significant modifications were observed in both theta and beta band. Compared to STAI-T– participants, STAI-T+ participants showed a decrease of theta connectivity between right mPFC and right PCC/Rsp (T= -3.93, $p= 0.011$; **Figure 2A**). Furthermore, compared to STAI-T– participants, STAI-T+ participants showed a decrease of beta connectivity between right mPFC and right ACC (T= -3.62, $p= 0.041$; **Figure 2B**). No significant differences were observed in the other frequency bands.

Association among EEG functional connectivity data, STAI-T and GSI scores

Detailed correlations are reported in Table 3. STAI-T total score were negatively related with the strength of theta connectivity between right mPFC and right PCC/Rsp (*rho*= -0.44, $p= 0.002$; **Figure 2C**). STAI-T total scores were also negatively related with the strength of beta connectivity between right mPFC and right ACC (*rho*= -0.46, $p= 0.002$; **Figure 2D**). The association among STAI-T total scores, and EEG functional connectivity data were also significant after controlling for GSI, sex and age (respectively $r_p= -0.34$, $p = 0.022$ and $r_p= -0.37$, $p= 0.013$). EEG functional connectivity data were also significant associated with both STAI-T-D and STAI-T-ANX after controlling for depressive symptoms, sex and age (see **supplement Table 1**).

Discussion

The main aim of the present study was to investigate the association between trait anxiety and DMN EEG functional connectivity. Compared to low trait-anxiety participants, high trait-anxiety participants showed a decrease of theta connectivity between right mPFC and right ACC, and a decrease of beta connectivity between right mPFC and right PCC/Rsp. Furthermore, DMN functional connectivity strength was negatively related with STAI-T total score (i.e., lower connectivity was

associated with higher trait-anxiety), even when controlling for the presence of other variables (i.e., sex, age, and general psychopathology), which are known to be associated with trait-anxiety (Donner and Lowry, 2013; Goldberg et al., 2003; Weger and Sandi, 2018).

Our results are in line with previous fMRI studies reporting a decrease of DMN functional connectivity in individuals with high-trait-anxiety (Modi et al., 2015; Zidda et al., 2018). Our study differs from, and adds to, previous findings by investigating the association between DMN functional connectivity and trait anxiety using qEEG and controlling for potential confounding variables.

The DMN has been conceptualized as the set of brain areas that are consistently more activated during RS when the mind is free to wander, suggesting a functional role in spontaneous cognition (Buckner et al., 2008; Whitfield-Gabrieli and Ford, 2012). Conversely, this network usually exhibit a decrease of activity during specific attention-demanding or stimulus-dependent task (Buckner et al., 2008; Whitfield-Gabrieli and Ford, 2012). Our results seems to suggest that individuals with high trait-anxiety fail to synchronize DMN brain areas when they are in RS condition, which reflect brain intrinsic activity (Deco et al., 2011). This interpretation may be in line with the Attentional Control Theory (Eysenck et al., 2007), suggesting that individuals with high-trait-anxiety try to control situations as much as possible, allocating excessive attentional resources in order to detect potential threat-related stimuli. Consequently, their attention to the environment is constantly maintained at a higher level (Savostyanov et al., 2009), affecting cognitive performance and the ability to down-regulate negative emotions (Berggren and Derakshan, 2013).

Therefore, our results could reflect the neurophysiological substrate of top-down cognitive control deficit, which is considered a core feature of high-trait-anxiety (Berggren and Derakshan, 2013; Eysenck et al., 2007). Accordingly, we observed a decrease of theta and beta EEG connectivity, respectively between mPFC and both PCC/Rsp, and ACC, which are considered

critical brain areas for top-down control, including emotion regulation (Etkin et al., 2011; Leech et al., 2011; Nelson et al., 2014; Szczepanski and Knight, 2014).

For example, our data are in accordance with previous fMRI studies confirming the critical relevance of mPFC for top-down control in trait anxiety (Bishop et al., 2004; Hare et al., 2008; Kim et al., 2011). Furthermore, it is known that the connections between frontal sites and PCC/Rsp are strongly implicated in cognitive control (Leech et al., 2011; Nelson et al., 2014; Szczepanski and Knight, 2014). It has also been observed that theta band activities over the mPFC appear to reflect *"*a common computation used for realizing the need for cognitive control*"* (Cavanagh and Frank, 2014). Coherently, the decrease of theta connectivity during RS has been associated to persistent anxiety and excessive worry regarding bodily symptoms (Ahn et al., 2017), and, on the contrary, increase of theta coherence during RS has been related to positive emotional states and low anxiety/frustrations (Aftanas and Golocheikine, 2001) as well as to enhanced top-down control (Cardenas et al., 2018). It should be noted that previous studies also reported an opposite neurophysiological pattern (i.e., increase of theta connectivity) in RS patients generalized social anxiety disorder (Xing et al., 2017) as well as in health subjects during anxious rumination. However, these discrepancies may be explained by several differences in study designs (e.g., RS vs rumination tasks) and methods, such as (i.e., ROIs selection). For example, compared to the present study, these previous reports investigated EEG coherence among all scalp electrodes (Xing et al., 2017), or among different pooled scalp electrodes (e.g., left and right centro-parietal area; Xing et al., 2017).

From a neurophysiological point of view, it is also known that symptoms related to impaired self-control (e.g., emotional dysregulation) involve reduced activity and connectivity in ACC and adjacent mPFC (Tang et al., 2016). Consistently, in a RS EEG study in a non-clinical sample, it has been observed (Farina et al., 2018) the association between decreased mPFC/ACC beta connectivity and both increased psychopathology (including anxiety symptoms) and increased impairment in higher-order integrative mental functions (i.e., mentalization, Adenzato et al., 2017). Finally, it is

interesting to note that we observed a decrease of EEG connectivity in the right hemisphere only. This may be in line with the predominant role of the right hemisphere in emotion processing and regulation (Reiser et al., 2012).

Although this interpretation may be interesting, it is important to note that it remains partially speculative due to the absence of emotional/cognitive control tasks in the present study. It is also important to consider some limitations in generalizing our results. One limitation is the small sample size which makes it difficult to draw definitive conclusions. Secondly, our sample included mostly female participants; this should be considered because some gender differences in RS brain EEG connectivity have been previously reported (Miraglia et al., 2015). Furthermore, we used scalp EEG recordings, which have an intrinsic limit in space resolution. Finally, similar to several previous neuroimaging (Yin et al., 2016; Zhang et al., 2016) and EEG studies (Aftanas and Pavlov, 2005; Aftanas et al., 2003; Knyazev et al., 2008; Putman, 2011; Takacs et al., 2015) we did not assess state variation of anxiety, which make our interpretation specific to trait anxiety. The relationship between brain activity with trait and state anxiety remain unclear (Tian et al., 2016) and is characterized by several methodological issue (e.g., administering the survey during neurophysiological assessment) (Etkin et al., 2004). Therefore, further longitudinal research using a test-rest paradigm (Tian et al., 2016) should be implemented in order to clarify the association between DMN functional connectivity and both trait and state anxiety. Moreover, future studies should investigate DMN connectivity underlying both trait anxiety and trait fear using well-validated instruments. Indeed, although previous research suggest that existing measures share a significant content overlap across both constructs, trait anxiety and trait fear reflect different emotions with separable behavioural (e.g., hypervigilance and prolonged hyperarousal vs avoidance behaviours across several situations) and neurobiological (e.g., increased left frontal hemispheric activity, whereas trait fear is characterized by increased right hemispheric activity) correlates (Sylvers et al., 2011).

Despite these limitations, to the best of our knowledge, this is the first study which investigated the association between DMN EEG functional connectivity and trait anxiety using an accurate and validated tool (i.e., eLORETA) to localize sources of electric activity in the brain and controlling for potential confounding variables. In conclusion, our results suggest that individuals with high-trait anxiety fail to synchronize DMN during RS, reflecting a possible top-down cognitive control deficit.

Our results could have also some clinical and therapeutic implications. Understanding individual differences in functional brain networks associated with trait anxiety is considered a crucial aim in the prevention and in early etiology understanding of clinical anxiety and related sequelae (Miskovich et al., 2016; Modi et al., 2015). Furthermore, our data highlights the utility of seseveral therapeutic approaches, such as transcendental meditation practice, which are known to modify EEG brainwave patterns (e.g., increase of RS theta coherence) and decrease trait anxiety levels (Orme-Johnson and Barnes, 2014). Therefore, it could be interesting to evaluate the consequence of effective therapeutic intervention of trait anxiety on DMN EEG functional connectivity to support these preliminary results.

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Table 1. Cortical 12 regions of interest.

ROIs	eLORETA MNI and Talairach coordinates[1]			Anatomical regions	Brodmann areas
	x	*y*	*z*		
1	-30 -30	40 40	25 21	Left mPFC	8-9-10
2	20 20	35 35	30 26	Right mPFC	8-9-10
3	-45 -45	-15 -16	-25 -20	Left Temporal Lobe	21-28-36
4	55 54	-15 -15	-20 -16	Right Temporal Lobe	21-28-36
5	-5 -5	-5 -3	35 32	Left PCC	23-24
6	5 5	-10 -8	30 28	Right PCC	23-24
7	-5 -5	30 30	20 17	Left ACC	32
8	5 5	30 30	20 17	Right ACC	32
9	-5 -5	-55 -52	25 26	Left PCC/Rsp	29-30-31
10	5 +5	-50 -47	25 25	Right PCC/Rsp	29-30-31
11	-45 -45	-50 -47	40 39	Left TPJ	39-40
12	45 45	-50 -47	35 35	Right TPJ	39-40

Note: [1]coordinates referred to the ROI centroid

Abbreviations: ROIs = Regions of Interest; eLORETA = exact Low Resolution Electric Tomography software; MNI = Montreal Neurological Institute; mPFC = Medial Prefrontal Cortex; PCC = Posterior Cingulate Cortex; ACC = Anterior Cingulate Cortex; PCC/Rsp = Posterior Cingulate/Retrosplenial cortex; TPJ = temporoparietal junction

Table 2. Demographic and clinical data of participants (N = 47).

	STAI-T+ (n=23)	**STAI-T– (n=24)**	**test**	***p***
Variables				
Age - *M (SD)*	22.30 ± 2.10	22.79 ± 2.50	Z-test = 0.80	0.55
Educational level (years) – M ± SD	15.83 ± 1.78	15.58 ± 1.93	Z-test = 0.53	0.94
Women - N (%)	19 (82.6 %)	16 (66.7 %)	$\chi^2_1 = 1.57$	0.21
STAI-T Total Scores - *M (SD)*	53.39 ± 7.06	35.33 ± 6.11	Z-test = 3.43	**< 0.001**
GSI - *M (SD)*	0.68 ± 0.51	0.32 ± 0.24	Z-test = 1.57	**0.015**

Note:
STAI-T = State-Trait Anxiety Inventory-Trait version; STAT-T+ = participants with high-trait-anxiety; STAT-T– = participants with low-trait-anxiety individuals; GSI = Global Severity Index

Table 3. Values of Spearman's rho correlation coefficient among EEG connectivity data, STAI-T (N = 47). Significant correlations are indicated by stars (*).

	STAI-T total scores	**GSI**	**Theta mPFC- PCC/Rsp**	**Beta mPFC- ACC**
STAI-T total scores	-			
GSI	0.59***	-		
Theta mPFC- PCC/Rsp	-0.44**	-0.18	-	
Beta mPFC- ACC	-0.46**	-0.21	0.49***	-

ote: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$
bbreviation;
'AI-T = State-Trait Anxiety Inventory-Trait version; GSI = Global Severity Index; mPFC = Medial Prefrontal Cortex; PCC/Rsp = sterior Cingulate/Retrosplenial cortex; ACC = Anterior Cingulate Cortex

Legend to figure
Figure 1. Participants flow diagram

Abbreviation:
STAI-T = State-Trait Anxiety Inventory-Trait version; STAI-T+ = participants with high-trait-anxiety; STAI-T– = participants with low-trait-anxiety

Figure 2. Decreased EEG functional connectivity and association with trait anxiety. (**A**) Results of the eLORETA between comparisons in theta frequency band in the right hemisphere. Threshold values (T) for statistical significance (corresponding to $p < 0.05$ and $p < 0.01$) are reported in the center of the figure. Compared to STAI-T– participants, STAI-T+ participants showed a decrease (blue line) of theta connectivity between right mPFC and right PCC/Rsp. (**B**) Results of the eLORETA between comparisons in beta frequency band in the right hemisphere. Compared to STAI-T– participants, STAI-T+ s participants showed a decrease of beta connectivity between right mPFC and right ACC. (**C**) Scatterplot of the correlation between trait anxiety and theta connectivity between right mPFC and right PCC/Rsp. (**D**) Scatterplot of the correlation between trait anxiety and beta connectivity between right mPFC and right ACC.

Abbreviation:
eLORETA = exact Low Resolution Electric Tomography software; mPFC = medial Prefrontal Cortex; PCC/Rsp = Posterior Cingulate/Retrosplenial cortex; ACC = Anterio Cingulate Cortex; STAI-T = State-Trait Anxiety Inventory-Trait version; STAI-T+ = participants with high-trait-anxiety; STAI-T– = participants with low-trait-anxiety