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Anxiety in Parkinson's disease: a resting-state high density EEG study

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Running title: EEG study of anxiety in Parkinson's disease

Abstract

Objective

To identify markers of Parkinson's disease (PD) related anxiety, using high density electroencephalography (hd-EEG).

Methods

108 patients participated in the study. They were divided into two groups: with and without clinically relevant anxiety, according to their score on the Parkinson Anxiety Scale. Resting-state hd-EEG was recorded. Spectral and functional connectivity characteristics were compared between the two groups.

Results

Thirty-three patients (31%) had significant anxiety symptoms. In the spectral analysis, relative power in the alpha1 frequency band in the right prefrontal cortex was lower in patients with anxiety than without. Functional connectivity analysis showed a stronger connectivity between the left insula and several regions of the right prefrontal cortex in patients with anxiety than in those without.

Conclusion

This study shows the pivotal role of the insula and frontal cortex in the pathophysiology of anxiety in PD and extends the results of previous studies using magnetic resonance imaging or positron emission tomography imaging.

Keywords: Anxiety disorders, Electroencephalography, Functional connectivity, Spectral analysis.

Introduction

Parkinson's disease is characterized by motor but also non-motor symptoms. Among the latter, anxiety is frequent with a mean prevalence of about 31% [6]. While several methods have been used to investigate the underlying mechanisms, they remain largely poorly understood. Structural magnetic resonance imaging (MRI) studies have shown correlations between the severity of anxiety and the volume of the amygdala as well as with cortical thickness of the bilateral frontal cortex, precuneus and anterior cingulate cortex [9,45,47]. Task-based and resting-state (rs) functional MRI studies have identified disturbances in the fronto-limbic networks, resulting in limbic and paralimbic hyper-reactivity in emotion processing areas, such as the amygdala and the insula. Another finding was aberrant activation in regions known to regulate emotional reactivity, such as the dorsolateral prefrontal and the cingulate cortex [7,9,15,38]. Using positron emission tomography (PET), Wang et al. [46] showed that anxiety in PD was associated with hypometabolism of the prefrontal cortex, suggesting a loss of voluntary control of emotion.

Apart from the amygdala, all these studies highlighted the predominant role of different cortical regions, such as the prefrontal cortex. Electroencephalography (EEG), is less stressful for the patient, and more repeatable than imaging techniques, and provides a direct measure of the neural activity of the cortex. It is therefore a useful technique to investigate markers of anxiety disorders. Furthermore, with a temporal resolution in the order of a millisecond, EEG assesses the fast and lagged spontaneous brain activity in time and frequency enabling the characterization of intrinsic neurocognitive networks. EEG has not previously been used to explore the cortical basis of anxiety disorders in patients with PD. Sachs et al. [40] have compared EEG patterns in non-parkinsonian subjects suffering from social phobia and healthy controls (HC). They reported a decrease in absolute and relative power in the delta, theta and slow beta frequency bands as well as an increased in power in the intermediate beta band in the patient group. Moreover, trait anxiety scores correlated positively with the dominant alpha frequency. In terms of functional connectivity, a higher connectivity in the theta band in non-parkinsonian subjects with generalized anxiety relative to HC group during rest was described by Xing et al. [48].

The aim of this study was to identify changes associated with PD-related anxiety by comparing EEG spectral patterns and functional resting-state networks in patients with and without anxiety disorders.

Methods

Study population

The data came from a previously published cross-sectional observational study [14] and were used by Carey et al. [9] for the identification of MRI markers of PD-related anxiety. One hundred and fifty-six patients were recruited from two movement disorders clinics in Lille (France) and Maastricht (The Netherlands). PD was diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria [20]. Dementia and any other neurological disorders were exclusion criteria.

The Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) was used to assess the severity of motor and non-motor symptoms. Disease severity was evaluated by Hoehn and Yahr stage.

The levodopa equivalent daily dosages (LEDD) were calculated [44] and the use of antidepressant and anxiolytics treatments reported. Anxiety was assessed using the Parkinson Anxiety Scale (PAS) [26], depression by the Hamilton Depression Rating Scale (HAMD) [18], apathy by the Lille Apathy Rating Scale (LARS) [42] and overall cognition by the Mattis dementia rating scale (MDRS) [31].

Patients were categorized as having (Anx+) or not (Anx-) clinically relevant anxiety symptoms according to their score on the PAS. Patients were allocated to the Anx+ group if their score in one of the three subscales of the PAS was above the cut-off values that were fixed at 9 for persistent anxiety (PAS_A), 3 for episodic anxiety (PAS-B) and 3 for avoidance behavior (PAS_C).

After explanation of the procedure, written informed consent was obtained from the participants. The study was approved by the institutional ethics committees (Lille: CPP Nord-Ouest IV, 2012-A 01317-36, Maastricht: NL56176.068.16)."

EEG Acquisition and preprocessing

Patients were investigated after receiving their usual antiparkinsonian treatment, using a 128-channel system (ANT Software BV, Enschede, the Netherlands), with 122 EEG scalp electrodes (Ag/AgCl), organized according to the 10/05 system [35]. For all patients, acquisitions were carried out at the end of the morning to limit sleepiness.

The protocol consisted of a 10-minute eyes-closed resting-state recording. An investigator monitored the subject and EEG and verbally alerted the subject every time there were EEG or behavioral signs of sleepiness. Samples of EEG with signs of sleepiness (slowing of background) were excluded off-line from the analysis.

Signal was sampled at a frequency of 512 Hz. Electrode impedances were kept below 10 kΩ. FCz and CPz electrodes were placed as reference and ground electrodes, respectively.

BrainVision Analyzer software (BrainProducts GMBH, Gilching, Germany) was used for signal preprocessing with the following steps: averaging to the common reference, ocular artefacts correction and 50-Hz filtering.

Muscle activity was removed by applying a 90 μV threshold. Finally, a 4-second epoch segmentation was performed.

EEG analysis

In order to explore group differences in the EEG patterns, two methods were used: spectral decomposition and functional connectivity analysis.

Spectral power

Spectral power analysis using Fast Fourier Transformation with a 2-second duration and 50% overlap, was applied on the scalp signals using the EEGLAB toolbox [12]. Absolute powers were evaluated in six frequency bands: delta (1-4 Hz), theta (4-7 Hz), alpha1 (8-10.5 Hz), alpha2 (10.5-13 Hz), beta1 (13-20 Hz) and beta2 (20-30 Hz) and averaged for each EEG channel. Based on these absolute power values, relative powers were estimated by normalizing each value by the sum of the powers in all the included frequency bands. Thereafter, only relative powers were considered for comparisons.

Two other measures were also considered: the peak of the background rhythm, defined as the frequency having the maximum power of the alpha rhythm on the posterior electrodes P3, P4 and Oz [30], and the spectral ratio between the power in the alpha and theta frequency bands.

The electrodes were separated into five regions of interest (ROI): frontal (34 electrodes), central (20 electrodes), parietal (14 electrodes), occipital (22 electrodes) and temporal (26 electrodes), following the anatomical correlations made on MRI of cortical projections [23]. Each region was divided into right and left sides. The remaining six electrodes (Fpz, Fp1, Fp2, Iz, I1, I2), located at the margin of the anatomical brain regions, were not considered for the analysis.

Functional connectivity

Functional connectivity between cortical areas was measured at the source level. The inverse problem was solved, using the weighted Minimum Norm Estimate (wMNE) method [28], using an average template, available in the Brainstorm toolbox [43], in order to reconstruct the temporal dynamics of the cortical regions. The source signals were then projected on the 68 ROIs of the Desikan-Killiany atlas [13]. Matrices of functional connectivity between the reconstructed sources were computed in the different frequency bands via the Phase Locking Value (PLV) method [24] using the EEGNET toolbox [19]. This measure quantifies the interaction between two oscillatory signals through the estimation of the phase relationships.

Statistical analyses

Demographic and clinical data

Demographic and clinical data were compared using the chi-square test for the qualitative variables and using two sample t-tests or Mann-Whitney tests, depending on normality of the distribution, for the quantitative variables.

All variables that were significantly different between the Anx+ and Anx- groups, except those related to anxiety, were used as co-variates in the following analyses.

Spectral power

Between-group comparisons of the relative spectral analysis values, global and region, were performed using analysis of covariance (ANCOVA). Multiple

comparisons corrections were applied using false discovery rate method. For each case, global values and lobes values, the six p-values obtained for the six considered frequency bands were adjusted. In case of significance, associations between the spectral values and the anxiety scores (PAS and PAS_A, PAS_B and PAS_C sub-scores) were investigated using multiple regressions.

All the analyses were performed with the XLStat software (Addinsoft. XLSTAT 2019: Data Analysis and Statistical Solution for Microsoft Excel. Paris, France).

Functional connectivity

Hypothesis tests on functional connectivity matrices were based on the network-based statistics (NBS) Toolbox from [49]. This toolbox implements two different analysis methods. Both were considered in this study. The first is the NBS method that enables rejection of the null hypothesis at the network level while controlling for the family-wise error rate (FWER). Statistical significance is estimated for subsets of mutually connected network nodes in topological rather than physical space. The NBS method comprises four steps. Firstly, the t-statistic for each individual edge in the connectivity network is calculated. For the experiments in this study, a threshold t-score of 3 was chosen. Secondly, a primary component forming threshold ($p<0.05$) is applied to identify edges displaying differences. Thirdly, sub-threshold edges were assessed for mutual connections forming clusters in topological space. Fourthly, a test with 5000 random permutations was applied to compute statistical significance for all previously identified network components.

The second analysis method in the NBS toolbox, the false discovery rate (FDR) [16], is more sensitive to focal effects involving single, isolated connections. It enables rejection of the null hypothesis at the level of specific connections, while controlling for the false discovery rate. In our study, 5000 permutations were used and significance threshold set to $p<0.05$.

In both analyses and as previously, the co-variates were introduced in the design matrix. The Brain Connectivity Toolbox (BCT) [39] was used to create three-dimensional graph visualizations, which represented below p-threshold connection pairs surviving multiple comparison correction.

Results

Demographic and clinical characteristics

EEG data were available for 108 patients. Their demographic and clinical characteristics are described in Table 1.

Gender, Hoehn & Yahr stage as well as the Mattis dementia rating scale were considered as co-variates.

Table 1: Demographic and clinical characteristics of the patients included in the study

	Patients without anxiety (n = 75)	**Patients with anxiety (n = 33)**	**p-value**
Demography			
Center: Lille (n = 57)	36 (48%)	21 (63.64%)	0.363
Maastricht (n = 51)	39 (52%)	12 (36.36%)	
Age (Years)	64.86 ± 8.65	65.93 ± 7.01	0.533
Education Duration (Years)	12.49 ± 3.58	11.73 ± 3.56	0.307
Sex-ratio (Male/Female)	2.95	1.06	**0.032**
Clinic			
Disease duration (Years)	7.83 ± 5.08	9.76 ± 7.26	0.173
Hoehn & Yahr stage	2 (0 – 3)	2 (2 – 3)	**0.002**
MDS-UPDRS part 1			
1.3. Depressed mood	0 (0 – 4)	1 (0 – 4)	**0.001**
1.4. Anxious mood	0 (0 – 4)	2 (0 – 4)	**< 0.0001**
1.7. Night-time sleep problems	2 (0 – 4)	2 (0 – 4)	**0.03**[*]
1.8. Daytime sleepiness	2 (0 – 4)	2 (0 – 4)	0.26
1.9. Pain and other sensations	1 (0 – 4)	2 (0 – 4)	**< 0.0001**
MDS-UPDRS part 3 (/132)	27.16 ± 11.91	30.97 ± 12.46	0.134
Hamilton depression rating scale (/54)	4.48 ± 3.48	8.97 ± 5.58	**< 0.001**
Lille apathy rating scale (/36)	-26.33 ± 6.18	-22.36 ± 7.49	**0.004**
Parkinson anxiety scale total (/48)	3.69 ± 2.87	14.79 ± 4.69	**< 0.0001**
Part A (/20)	2.85 ±2.87	9.47 ± 4.32	**< 0.0001**
Part B (/16)	0.42 ± 0.85	2.38 ± 2.26	**< 0.0001**
Part C (/12)	0.43 ± 0.85	2.94 ± 2.32	**< 0.0001**
Mattis Dementia rating scale (/144)	138.43 ± 4.82	136.03 ± 5.44	**0.016**
Medications			
LEDD (mg / day)	706.98 ± 515.62	960.70 ± 553.80	**0.023**
Antidepressants (n = 18)	5 (6.67%)	13 (39.39%)	**< 0.001**
Anxiolytics (n = 12)	3 (4.00%)	9 (27.27%)	**0.001**

MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale. LEDD: Levodopa Equivalent Daily Dose.

Spectral analysis

The global relative spectral power in the different frequency bands is presented in Table 2 and showed no significant difference between groups. The cortical topography of the relative spectral power observed in each group is depicted in

Figure 1 and shows a global decrease in the alpha band and an increased in the beta2 and delta bands for the Anx+ group, possibly more marked in the anterior part of the right hemisphere. Regional analyses confirmed a significant decrease of alpha1 power in the right frontal region ($p_{uncorrected}$=0.04, $p_{corrected}$=0.042) (Figure 2).

Table 2: Comparison of the global relative spectral power in the different frequency bands between the two patient groups.

	Patients without anxiety	Patients with anxiety	p-value
Delta	0.11±0.02	0.12±0.04	0.37
Theta	0.20±0.06	0.20±0.07	0.96
Alpha1	0.19±0.05	0.17±0.05	0.13
Alpha2	0.12±0.03	0.11±0.02	0.32
Beta1	0.19±0.03	0.18±0.03	0.50
Beta2	0.16±0.03	0.18±0.05	0.28

The posterior background rhythm was at a peak frequency of 8.63 ± 1.19 Hz for the Anx- group and 8.55 ± 1.20 Hz for the Anx+ group (p=0.75).

There was no significant group difference regarding the spectral ratio between the alpha and theta bands (p=0.11).

Multiple regression analyses were carried out to examine associations between the alpha1 power in the right frontal region and the PAS scores and sub-scores. They revealed a significant association with avoidance behavior (PAS_C, β=-0.20, p=0.035). There was a trend toward a significant association for episodic anxiety (PAS_B, β=-0.15, p=0.06), while no associations were found for persistent anxiety (PAS_A, p=0.62) and the total scale (p=0.18).

Functional connectivity

Global Network level

The NBS method analysis revealed no significant between-group differences when comparing the complete network connectivity matrices in the different frequency bands.

Regional level

The FDR method revealed significantly stronger connections involving the left insula in the Anx+ group than in the Anx- group (table 3). In the theta band, this between-group difference concerned connections of the left insula with the right frontal,

including the rostral middle, the pars opercularis, the pars triangularis and the pars orbitalis regions and the cingulate cortices. In the alpha band, it concerned the connection linking the left insula with the right isthmus cingulate cortex. In the beta2 band, a single connection linking the left insula and the rostral middle frontal cortex was implicated.

We also looked for connections that showed a trend towards a significant difference between the two groups, by considering connections with t-values close to those described above. This identified the connection between the left insula and right isthmus cingulate cortex in the beta1 and beta2 bands as well as the connection between the left insula and the right rostral middle frontal cortex, in the alpha2 and beta1 bands. New regions also appeared, thus, in the theta band, connections linking the left insula to the right precentral and the right temporal lobes as well as the right fusiform appeared stronger in the Anx+ group. This last connection appeared stronger also in the alpha2 band. Complete description of these results is summarized in Table 3 with the corresponding t-values, and illustrated in Figure 3.

Table 3: Connections between cortical regions of the Desikan-Killiany atlas for which significant (bold) or trend towards significant (italics) difference (Anx+ > Anx-) was found by the false discovery rate method.

Region 1	Region 2	t values
Theta band		
Left insula	**Right rostral middle frontal**	**3.94**
Left insula	**Right pars opercularis**	**3.52**
Left insula	**Right pars triangularis**	**3.38**
Left insula	**Right pars orbitalis**	**3.15**
Left insula	**Right isthmus cingulate**	**3.76**
Left insula	*Right precentral lobe*	*2.95*
Left insula	*Right temporal lobe*	*3.05*
Left insula	*Right fusiform*	*3.02*
Alpha1 band		
Left insula	**Right isthmus cingulate**	**3.93**
Alpha2 band		
Left insula	**Right isthmus cingulate**	**4.27**
Left insula	*Right rostral middle frontal*	*3.10*
Left insula	*Right fusiform*	*3.08*
Beta1 band		
Left insula	*Right rostral middle frontal*	*3.10*
Left insula	*Right isthmus cingulate*	*3.00*
Beta2 band		
Left insula	**Right rostral middle frontal**	**3.85**
Left insula	*Right isthmus cingulate*	*3.03*

Parkinson's disease patients with (Anx+) or without (Anx-) clinically relevant anxiety.

Discussion

Main outcomes

The objective of this study was to identify EEG signatures of PD-related anxiety. High resolution EEG acquisitions were used allowing the reconstruction of cortical sources. Thereafter, two approaches were considered: signal spectral decomposition and functional connectivity at the cortical level. The findings of the spectral analysis show that anxiety is associated with changes in the alpha activity in the right frontal cortex, and the connectivity analysis shows that the functional connectivity between the left insula and the areas of the right frontal and cingulate cortex is increased in the theta, alpha and beta-2 band. Using MRI on the same study population [9], we found cortical thinning in the prefrontal, parietal left cingulate cortices in the group of PD patients with anxiety. We also found a deformation in the left amygdala in this group as well as a higher connectivity between the fear circuit and the salience network and a lower connectivity between the left frontoparietal attentional and language networks. The results of our EEG study bring new insights about the mechanisms of anxiety in PD.

Alpha activity changes

The main outcome of the spectral analysis was a statistically significant decrease of the relative power in the alpha1 band in the right frontal region in the Anx+ group. Figure 1 reveals that this decrease seems to be rather global, with a predominance in the right lobe, in the alpha bands (alpha1 and 2), while a power increase in the delta band was also observed for this group. Activity in the alpha frequency band is the most common component of human brain activity [4]. It is modulated by sensory, motor and cognitive processes [1]. At rest, alpha activity is generally low in the frontal region. It increases with increased cognitive load [3]. Cognitive impairment is generally associated with a decrease in resting-state alpha power [27].

Very few studies have used EEG to explore anxiety and the reported results have been poorly validated [34]. Nevertheless, some studies have reported an increase in

alpha oscillations in anxious individuals [22] or in patients with anxiety disorders [40,41]. This was interpreted as a manifestation of hyperarousal in anxious subjects. However, these data are from studies with small numbers of young participants, a very short period of recording in the resting-state condition, with a limited number of electrodes. The decrease in alpha power observed in the Anx+ group cannot be related to lower cognitive efficiency in this group since this factor was controlled. Moreover, despite a slight between-group difference at the Mattis dementia rating scale score, mean scores were high and dementia was an exclusion criterion. Several studies have shown that alpha power, particularly in the frontal regions, was modulated by attention. More specifically, an increase in alpha power could reflect the efficacy of attentional filtering when irrelevant information is inhibited and cognitive resources focused by internally oriented attention (top-down) [10,21]. In the Anx+ group, reduced alpha power in the frontal region could reflect the lower efficiency of this process. Due to altered representation of real or potential threats in their environment, anxious PD patients may allocate more attention to external bottom-up stimulation leading to a change in the distribution of alpha power.

Besides spectral power analyses, EEG rhythm modifications were also analyzed through the ratio between the alpha and theta bands and the peak of the posterior background rhythm. No between-group difference was observed. This supports the hypothesis that the alterations observed in anxious patients are not the result of a general brain slowing or a global cognitive deficit since changes in these parameters were reported as markers of cognitive decline and conversion to dementia in PD [33].

Increase of the functional connectivity of the left insula

In terms of functional connectivity, the network-based analysis did not reveal any specific difference in terms of clusters between the two groups while the FDR analysis, more suitable to detect local differences in single connections, brought out significant differences in the different frequency bands. All involved the left insula (Table 3 and Figure 3). In the theta band, connections between the left insula and the lateral prefrontal cortex (rostral middle, pars opercularis, pars triangularis and pars orbitalis) and the isthmus cingulate cortex were stronger in the Anx+ group. In the alpha bands, the connection between the left insula and the isthmus cingulate cortex was stronger in this group and, in the beta2 band, the connection between the left

insula and the rostral middle frontal cortex (dorso-lateral prefrontal cortex) was stronger. These results suggest that the left insula acts as a hub around which connections are strengthened in the Anx+ group. The insula plays a key role in anxiety since it conveys interoceptive information to medial prefrontal cortex [11]. It is part of a network involving the anterior cingulate cortex, the medial prefrontal cortex, the amygdala and other limbic structures [36]. The increased connectivity of the insula with the frontal cortex observed here in anxious PD patients could reflect a change in emotional information processing with more attention allocated to visceral changes caused by anxiety, contributing to its maintenance [37], and altered regulation of emotion by the prefrontal cortex [5]. The insula and the prefrontal cortex are densely interconnected with the amygdala [32]. Here, functional connectivity analysis was limited to cortical areas, since localization of sub-cortical sources, while possible, remains the subject of many reservations. Nevertheless, the reported results are in line with the increased connectivity between the fear and salience circuits, described in rs-fMRI on the same study population [9]. Changes in this functional circuit were also reported by Wang et al using PET-FDG.

There was also an increased connectivity between the insula and the posterior cingulate cortex in several frequency bands in the Anx+ group. This region, with the precuneus to which it is very close, is involved in self-awareness [17]. Through its connections with the hippocampus, it can play a role in anxiety via learning / memory mechanisms or the establishment of avoidance behaviors [2]. The increased connectivity observed here may be a marker of the maintenance of avoidance behaviors that characterize anxiety in PD [25].

Strengths and limitations of the study

The study was carried out with well-established protocols and techniques in terms of signal acquisition, preprocessing and processing. The analysis scheme combined two different and complementary approaches, scalp signal spectral decomposition and source-connectivity analysis, for a full understanding of the changes, and the results are consistent. The resting-state protocol, in addition to allowing comparison with studies using different brain imaging methods, limits the influence of fatigue and does not require participation of the subject. Moreover, the combination of wMNE for the inverse problem resolution and sources localization and the PLV, as a similarity

measure for connectivity quantification, was reported as the most appropriate for a group comparison study [29]. Furthermore, the PLV is often said to be sensitive to volume conduction because this technique does not remove zero-lag connectivity. Moreover, it has recently been reported that PLV-based functional networks are significantly correlated with fMRI networks during resting state, while it was not the case for methods that remove zero-lag connections such as the PLI. Indeed, all zero-lag connections are not spurious.

Nevertheless, our study has several limitations. Firstly, among the 108 patients, only 33 had clinically relevant anxiety. The sample size of the two patient groups was thus unbalanced and this may have hampered the statistical analyses. A solution could have been the artificial matching of patients by randomly reducing the number of the patients in the Anx- group. We did not adopt this solution because our distribution (33 Anx+/75 Anx-) was close to the usually reported prevalence (31%) of anxiety in PD [6]. Additionally, the sample sizes were sufficient for most statistical methods and special attention was paid to the existence of outliers in the different analyses. Secondly, anxiety was here considered globally without distinction of the different anxiety subtypes (general anxiety, phobias, PD-specific anxiety disorders, etc). It is possible that there are specific markers for each subtype and further studies are needed to identify them. Thirdly, although our analyses were adjusted for several demographic and clinical variables, our patient groups differ in terms of severity of depressive symptoms, apathy and medication status. We decided not to adjust for these variables in order not to excessively reduce the statistical power. Moreover, due to the overlap between depression and anxiety symptoms, it is quite logical that patients with anxiety had higher scores at the HAMD. Nevertheless, the scores were quite low and only a few patients had clinically relevant depression. The higher score at the LARS in the Anx+ group could also be explained by an influence of anxiety symptoms. Indeed, avoidance behavior may limit initiatives, and social phobia or PD-specific anxiety disorders may limit social interactions. The interactions between both syndromes are unknown and should be further explored.

Cognitive impairment is known to slow down the EEG signal and, more globally, to induce alterations in spectral parameters as well as functional connectivity. Overall cognitive efficiency was controlled in our study. Patients with mild dementia were excluded, but some participants had probable mild cognitive impairment. Table 1

shows that despite a slight but significant between-group difference, the mean score at the Mattis dementia scale was high in both groups, suggesting preserved efficiency, and, this factor was included as a co-variate in our analyses. Furthermore, the posterior background rhythm as well as the alpha/theta spectral ratio were not different between groups. These two parameters have been reported as markers of cognitive impairment in PD [33].

Regarding medication, the Anx+ group had a more severe PD as shown by the significantly higher Hoehn & Yahr stage and lower score on the Mattis dementia rating scale. A higher LEDD may thus be required to bring their motor scores back to the same level as the Anx- group. Patients in the Anx+ group had higher rates of benzodiazepine use. This could have influenced their EEG spectrogram (increased frontal beta powers caused by rapid rhythms induced by the treatment and slight decrease of alpha powers in posterior regions ([8]). However, the changes observed here did not correspond to this pattern.

Lastly, considering the connectivity analysis, only static patterns were estimated while one of the main advantages of EEG exploration, compared with imaging explorations, is its higher temporal resolution. EEG offers the possibility to dynamically measure the connectivity states. Although this approach seems to be more suitable for task-based explorations, it may be an interesting approach for further analyses to characterize the temporal course of the connections.

Conclusion

This study is the first to investigate the mechanisms of PD-related anxiety using high density resting state EEG. The reported results provide new insights, supporting findings of previous studies using other modalities, mainly rs-fMRI, and show that EEG could be a relevant technique to explore these disorders. However, in view of the lack of validated results about the modifications of EEG patterns in these disorders in general and the significance levels of the results of the current study, it seems imperative to confirm these outcomes with further works and by recruiting patients with a larger panel of anxiety disorders. The data used were from a cohort originally set up to study cognition, and some sub-types of anxiety disorders may not have been sufficiently represented.

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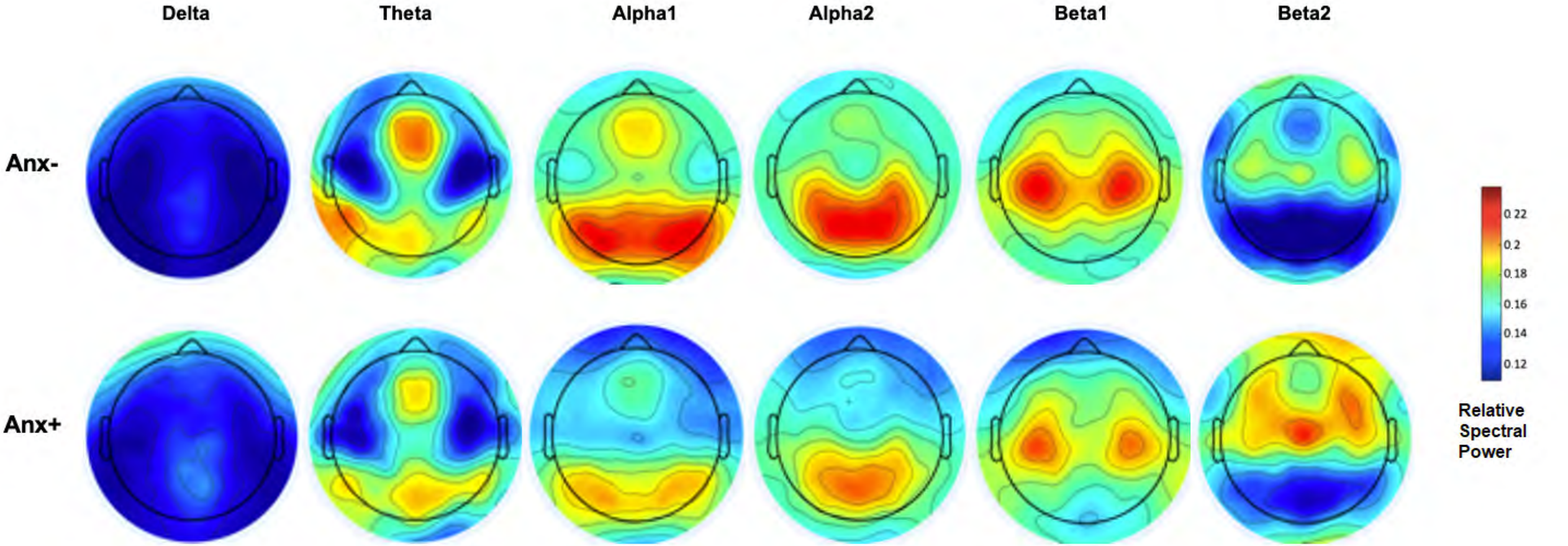
Figures legends

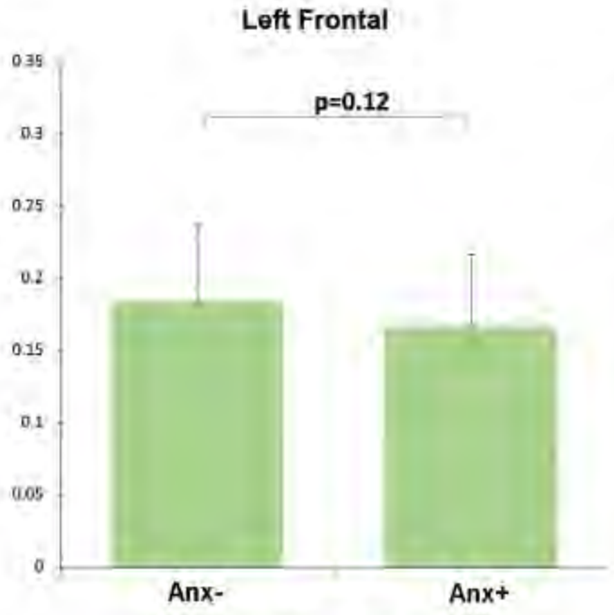
Figure 1: Topographical representation of the relative spectral power at the scalp level for each frequency band according to the group: Parkinson's disease patients with (**Anx+)** and without clinically relevant anxiety (**Anx-).**

Figure 2: Spectral relative powers distribution in the alpha1 band in the two patients' groups. Parkinson's disease patients with (**Anx+)** and without clinically relevant anxiety (**Anx-).**

Figure 3: Functional connectivity comparison results between Parkinson's disease patients with (Anx+) and without clinically relevant anxiety (Anx-). Connections quoted 1 to 5 (in bold) were statistically significantly stronger in Anx+ group in at least one of the considered bands (theta, alpha and beta). Connections not in bold showed a non-significant trend towards being stronger in the Anx+ group. (See table 3 for t-values of the connections).

Anx+: Parkinson's disease patients with clinically relevant anxiety and Anx-: Parkinson's disease patients without clinically relevant anxiety.


Delta
Theta
Alpha1
Alpha2
Beta1
Beta2
Anx-
Anx+
0.22
0.2
0.18
0.16
0.14
0.12
Relative
Spectral
Power


Left Frontal
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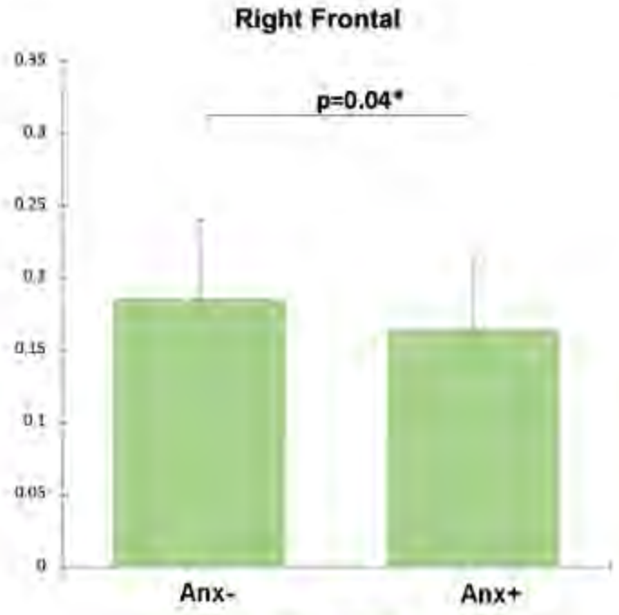
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
Anx-
Anx+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0.25
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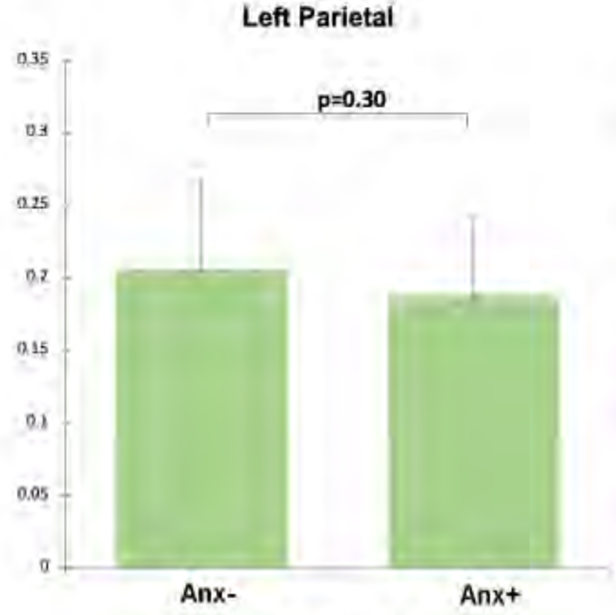
0.15
0.1
0.05
0
Anx-
Anx+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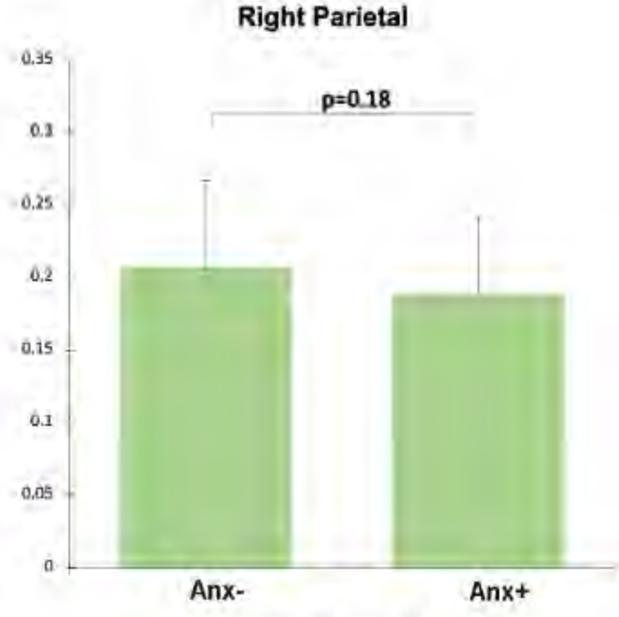
0.15
0.1
0.05
0
Anx-
Anx+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0.1
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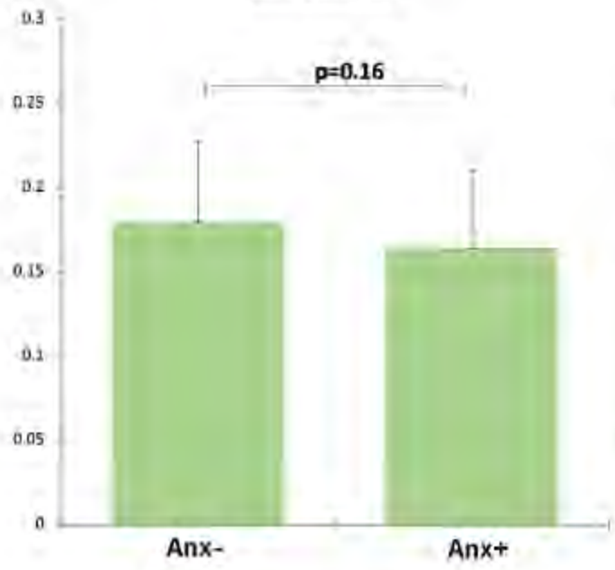
0
Anx-
Anx+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0.2
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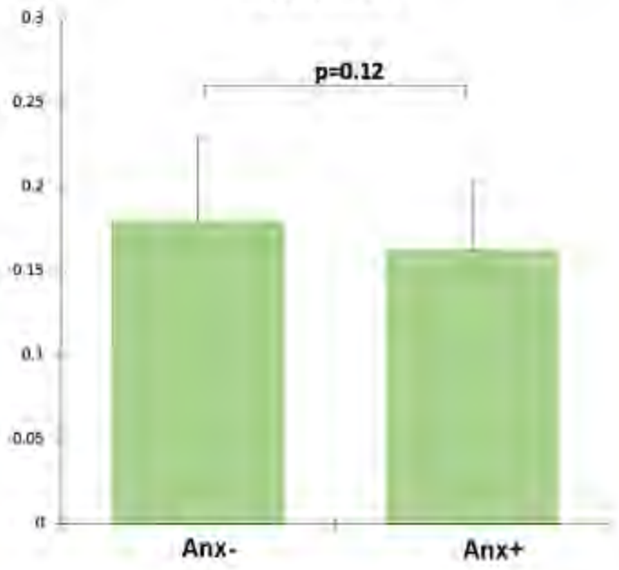
0.1
0.05
0
Anx-
Anx+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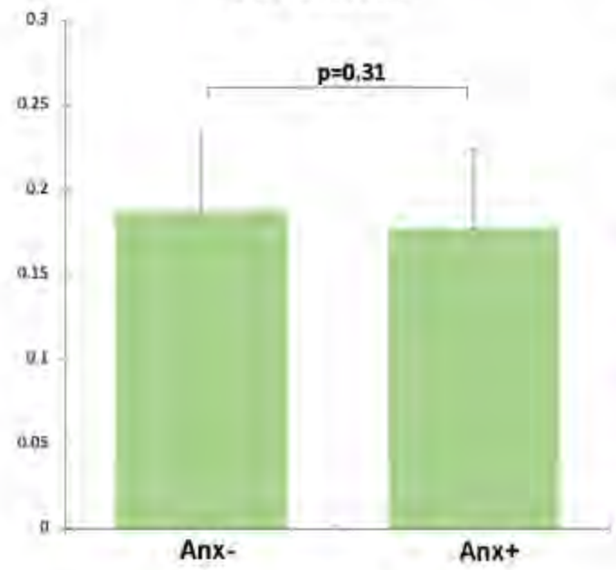
0
Anx-
Anx+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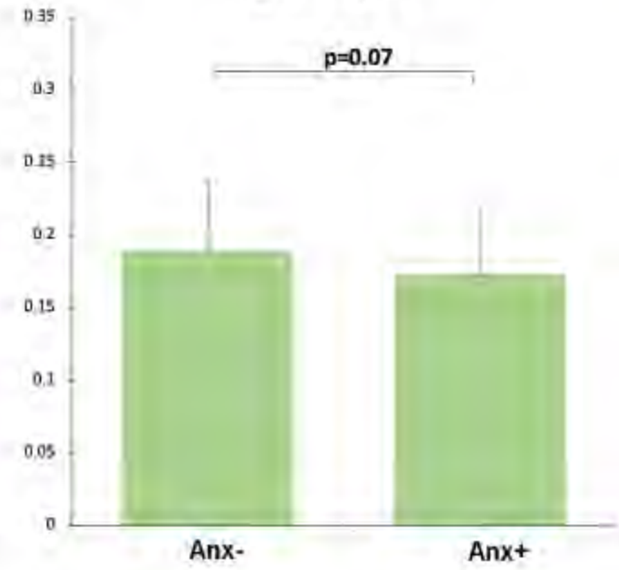
0.05
0
Anx-
Anx+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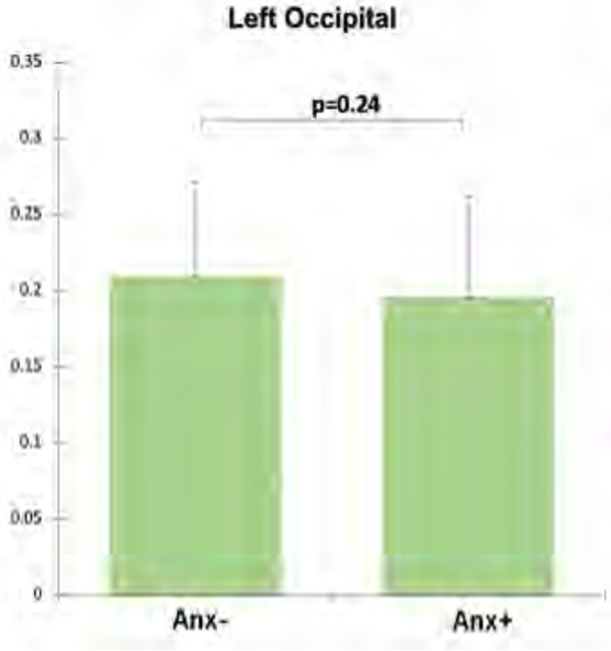
Anx-
Anx+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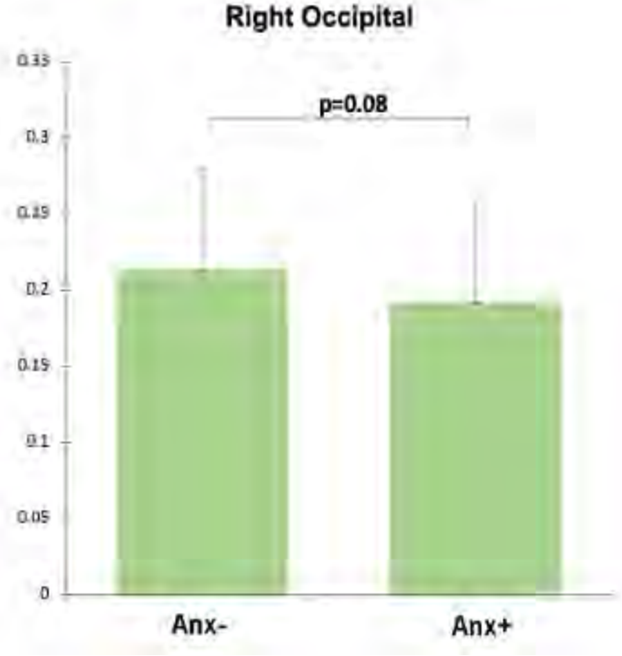
0
Anx-
Anx+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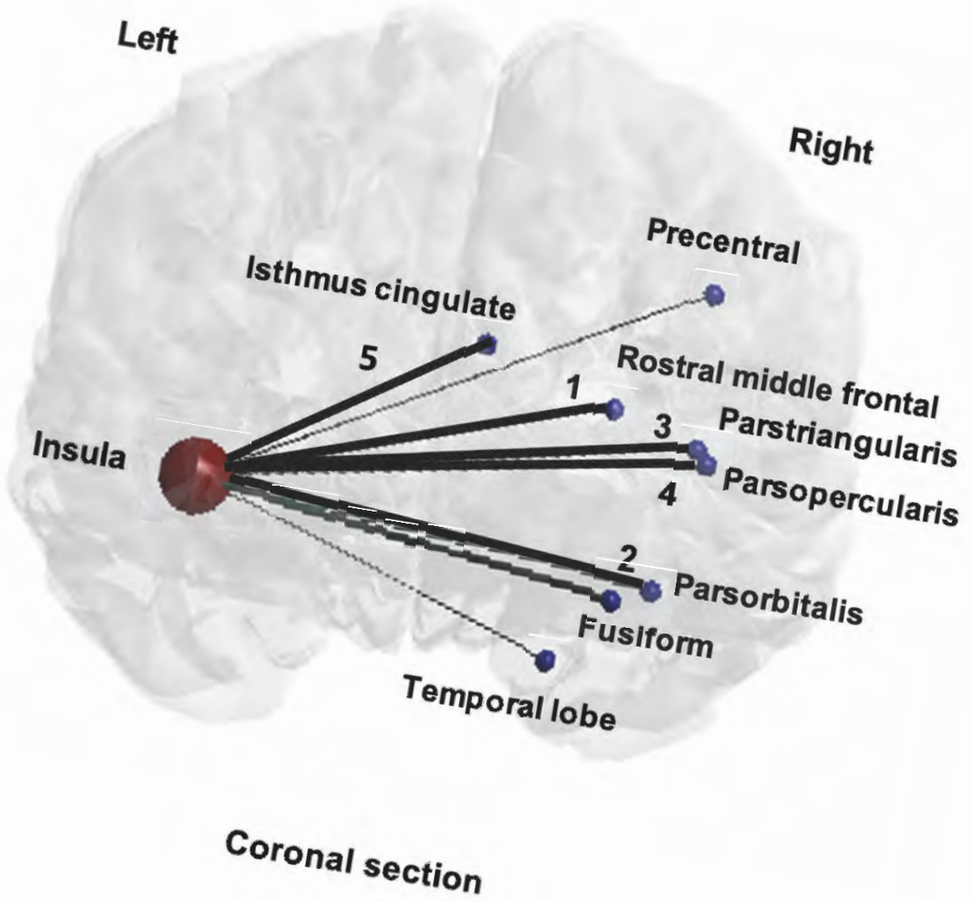
Anx-
Anx+



Coronal section