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Neuroimaging depression and anxiety in essential tremor: A diffusion tensor imaging study

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ABSTRACT

Objective: Patients with essential tremor (ET) may exhibit non-motor features, including those that are neuropsychiatric. Depression and anxiety are the most common among these. This study aims to investigate the possible relationship between microstructural brain changes and symptoms of depression and anxiety in ET.
Methods: We assessed 62 ET patients (40 women and 22 men, mean age 46.0 ± 20.4) for symptoms of depression and anxiety using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Thirty-two patients had severe or moderate symptoms of anxiety, and 15 patients had severe or moderate depressive symptoms. Microstructural brain changes were evaluated using diffusion tensor imaging (DTI), which was reported using fractional anisotropy (FA), mean diffusivity (MD), apparent diffusion coefficient (ADC), radial diffusivity (RD), and axial diffusivity (AD) values calculated for 17 regions of interest including the prefrontal cortex, paralimbic and limbic structures and cerebellar peduncles. We evaluated the relationship between observed changes in brain regions and symptoms of depression and anxiety.
Results: Decreased left amygdala FA ($p = 0.003$) and increased left amygdala RD ($p = 0.04$) were detected in depressed vs. non-depressed ET patients. Left ventrolateral prefrontal cortex (VLPFC) FA ($p = 0.02$) and left precuneus FA ($p = 0.02$) values differed between anxious patients vs. non-anxious ET patients. BDI scores were correlated with left amygdala FA and left RD, while BAI scores were correlated with left VLPFC FA and left precuneus FA.
Discussion: Our results provide evidence that symptoms of depression and anxiety could be based in structural brain changes observed in patients with ET.

1. Introduction

Essential tremor (ET) is one of the most common movement disorders, with an estimated prevalence of 4.0%–5.6% among individuals age ≥40 years. Its core motor feature is 4–12 Hz kinetic tremor [1,2]. Numerous studies have reported and focused on neuropsychiatric symptoms in ET [3,4], particularly depression and anxiety. Depression occurs in 30–40% of patients with ET [5–9] and ET patients more commonly manifest symptoms of anxiety than the normal population [10–16]. Social phobia has been observed as one of the most common forms of anxiety in ET [17,18]. Although these two symptoms are the most studied neuropsychiatric features in ET, it is still unclear as to whether these affective disturbances are associated with identifiable underlying brain changes or are merely a secondary psychiatric response to disabling tremor [19].

Affective disturbances such as anxiety and depression have been related to the cerebellum in the context of cerebellar cognitive affective syndrome (CCAS) [20,21], and the cerebellum appears to contribute

Abbreviations: ET, essential tremor; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; ADC, apparent diffusion coefficient; RD, radial diffusivity; AD, axial diffusivity; VLPFC, ventrolateral prefrontal cortex

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significantly to the neuropathology of ET [22,23]. Therefore, cerebellar connections to the paralimbic and limbic systems and prefrontal cortical areas via the cerebello-thalamo-cortical pathway may explain the underlying mechanism of depression and anxiety in ET [24–26]. Both depression and anxiety can be manifestations of CCAS.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that evaluates microstructural brain changes. This technique provides information about directional tissue integrity (fractional anisotropy-FA), tissue breakdown with increased water content (mean diffusivity-MD), and the integrity of axons versus their adjacent myelin sheaths (radial diffusivity-RD and axial diffusivity-AD), and apparent diffusion coefficient (ADC). DTI also shows where neuronal/axonal loss occurs as a result of neurodegeneration or inflammation. Decreased FA and increased MD, ADC, RD, AD values imply impaired tissue integrity, and the technique allows changes in tissue to be detected before reaching the macro scale [27].

To our knowledge, the microstructural brain correlations of depression and anxiety symptoms have not yet been studied in patients with ET. Our goal is to attempt to identify brain changes that are associated with depression and anxiety and to explore the neuroanatomical correlates of these symptoms.

2. Methods

2.1. Participants

Between August 2017 and July 2018, 102 ET patients were enrolled for the study after visiting the general neurology or movement disorders clinic at the Bezmialem Foundation University Hospital and Eyup Sultan Additional Building in Istanbul, Turkey. The evaluation consisted of a detailed physical and neurological examination, neuropsychiatric assessment and brain MRI. Inclusion criteria were: (1) ET according to diagnostic criteria of the Consensus Statement of the Movement Disorder Society on Tremor [28], (2) no contraindications to MRI (e.g. metal heart valve prosthesis, pacemaker), (3) no dystonic features, no parkinsonian signs, no clinical features rarely seen in ET such as clear asymmetry, and no signs of psychogenic tremor, (4) no history of any other neurological disease or neurological surgery (e.g. head trauma, stroke, brain surgery, epilepsy, etc.), (5) no psychiatric disorder other than depression or anxiety, (6) no history of debilitating chronic disease, and (7) no history of excessive ethanol or coffee consumption. Additionally, exclusions were made based on (i) a slit lamp examination in young ET patients to exclude Wilson's disease (age $<$ 45) and (ii) clinical dementia rating $>$ 0.5 in older patients (age $<$ 65), as calculated after detailed cognitive evaluation.

Eleven patients missed their appointments, could not be reached during the study period, or did not want to continue the study. After the MRI procedure, 2 patients with leukoencephalopathy, 1 patient with basal ganglia infarction, 5 patients with other vascular lesions, and 13 patients with motion/field of view issues were excluded. Eight patients with incomplete clinical data were also excluded. Sixty-two patients (40 female and 22 male) completed the full examination and were included the study.

The study was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and was approved by the Ethical Committee of the Bezmialem Foundation University Hospital. The full procedures were explained, and signed, informed consent was obtained from the participants.

2.2. Clinical and neuropsychiatric evaluation

Tremor was rated according to the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS). The FTMTRS includes ratings for resting, postural, and kinetic tremors. Part A includes ratings of tremor according to body region (Questions 1–9), and part B includes ratings of tasks performed with each hand (Question 10–13); both parts A and B are assessed by clinicians. Part C assesses the functional disability due to tremor severity (Question 14–21) as rated by patients. For each item, the scores range from 0 to 4 for a total score range of 0–84, with higher scores indicating more severe tremor [29].

The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to evaluate neuropsychiatric symptoms. The BDI consists of 21 statements related to aspects of depression which are rated from 0 to 3 for a maximum score of 63; higher scores indicate more depressive symptoms. Score ranges are as follows: 0–13 indicates minimal depression, 14–16 indicates mild depression, 17–29 indicates moderate depression, and 30–63 indicates severe depression. Turkish validity and reliability study of BDI was performed by Hisli et al. [30]. BAI similarly consists of 21 questions that measure the severity of anxiety (range 0 to 3 for each question) for a maximum score of 63 (higher scores indicate more anxiety symptoms). Score ranges are as follows: 0–7 indicates minimal level of anxiety, 8–15 indicates mild anxiety, 16–25 indicates moderate anxiety, and 26–63 indicates severe anxiety [31].

2.3. Neuroradiological evaluation

All cases underwent MRI and DTI from which FA, ADC, MD, and RD were measured from 17 regions of interest (ROI) in each brain hemisphere. These ROIs were selected based on their biological associations with depression and anxiety as well as those indicated in previous neuroimaging studies on ET. The following structures were assessed: anterior thalamic radiation, caudate nucleus, cerebellar peduncles (superior, middle, inferior), dorsolateral prefrontal cortex, ventrolateral prefrontal cortex (VLPC), orbitofrontal prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, stria terminalis, cuneus, precuneus, amygdala, hippocampus, parahippocampus, and insula.

MRI was performed on a 1.5 T system (Siemens, Avanto, Erlangen, Germany) with head coil. First, a routine brain imaging protocol included T1-weighted (T1W) spin echo (TR/TE, 460/14 ms), T1W with fat suppression (TR/TE, 715/7.5 ms) without contrast, T2-weighted (T2W) turbo spin echo (TR/TE, 2500/80 ms), FLAIR (TR/TE, 8000/90 ms) sequences. Then the 3D T1W volumetric sequences (TR/TE/TI, 12.5/5/450 ms) without contrast were applied using a magnetization-prepared rapid acquisition of gradient echo sequence (MPRAGE) with an isotropic voxel resolution of 1 mm. Parallel imaging by using generalized auto calibrating partially parallel acquisition (GRAPPA) with an integrated parallel acquisition technique (iPAT) factor of 2 was applied. The DTI included a single-shot, spin-echo, echo-planar sequence with TR/TE, 2700/89 ms; matrix, 128 × 128; field of view, 230 mm and slice thickness 5 mm and 34 diffusion-encoding directions were used at $b = 0\ s/mm^2$ and $b = 1000\ s/mm^2$. Parallel imaging by using GRAPPA with an iPAT factor of 3 was applied. The Leonardo console (software version 2.0; Siemens) was used for FA, ADC, MD and RD map reconstruction. The 3D T1W images were used as anatomic references for the placement and tracing of ROIs. These images were coupled with the corresponding region of FA, ADC, MD, RD maps at the same section level. All the ROIs were drawn manually in circular shapes with constant size. The adaptation of the sizes and placement of the ROIs were achieved through simultaneous assessment by experienced radiologists (OH, MD) according to *Dissecting the white matter tracts: Interactive Diffusion tensor imaging teaching atlas* [32] (Fig. 1).

2.4. Statistical analysis

Analyses were performed with SPSS 20.0 statistical software (IBM Corporation). Descriptive statistical methods (e.g. frequency, percentage, mean, and standard deviation) were used to describe the demographic characteristics of participants. Pearson chi square tests were used to compare categorical variables. Kolmogorov Smirnov test was used for the evaluation of normality. Independent sample *t*-tests (for normally distributed variables) and Mann-Whitney *U* tests (for

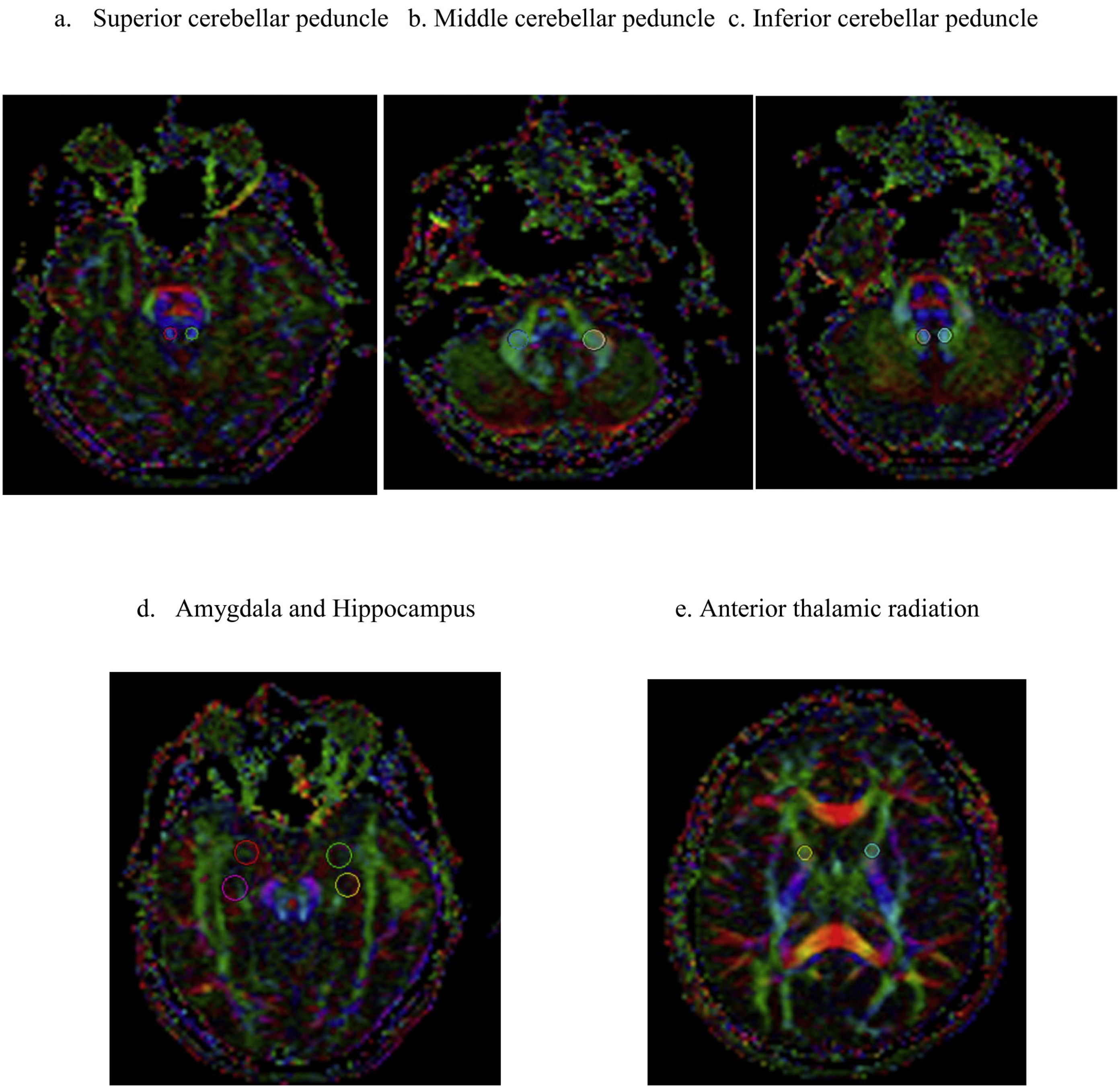

Fig. 1. Placement of the ROIs.

nonnormally distributed data) were used to compare DTI metrics between groups. Spearman correlation analyses were used to assess correlations between DTI metrics and BDI and BAI scores. Multiple linear regression analysis was used to evaluate the relationship between brain regions and test scores while adjusting for age and gender effects. A statistically significant difference was set at $p < 0.05$.

3. Results

3.1. Sociodemographic and clinical data

The mean age of enrolled subjects (n = 62, 40 female and 22 male) was 46.0 ± 20.4 years (Table 1). The mean tremor duration was 10.6 ± 9.8 years. Forty-five patients (72.6%) had a family history of ET. The mean FTM-TRS score was 23.3 ± 9.9. Fifty-two (83.9%)

Table 1
Demographic and clinical characteristics (n = 62).

	N %	Mean ± SD
Age in years		46.0 ± 20.4
Gender		
Female	40 (64.5%)	
Male	22 (35.5%)	
Years of education		
< 11 years	32 (51.6%)	
≥11 years	30 (48.4%)	
Tremor duration in years		10.6 ± 9.8
FTM-TRS score		23.3 ± 9.9
Family history of ET	45 (72.6%)	

Table 2
Clinical features of groups.

	Group D1 (N = 47)	Group D2 (N = 15)	p value (D1 vs. D2)	Group A1 (N = 30)	Group A2 (N = 32)	p value (A1 vs. A2)	Group A3 (N = 17)	p value (A1 vs. A3)
Age (years)	44.7 ± 20.6 MR = 30.5	49.9 ± 19.9 MR = 34.6	0.45[a]	47.7 ± 21.0 MR = 32.7	44.4 ± 19.9 MR = 30.4	0.62[a]	39.5 ± 19.2 MR = 21.29	0.31[a]
Gender			0.04			< 0.01		0.05
Female	27 (57.4%)	13 (86.7%)		16 (%53.3)	14 (46.7%)		4 (23.5%)	
Male	20 (42.6%)	2 (13.3%)		14 (%46.7)	16 (53.3%)		13 (76.5%)	
Tremor duration (years)	9.5 ± 8.5 MR = 26.8	14.3 ± 12.5 MR = 35.8	0.07[a]	7.9 ± 7.4 MR = 23.8	12.9 ± 10.9 MR = 33.4	0.03[a]	11.9 ± 9.7 MR = 25.6	0.13[a]
FTM-TRS score	22.1 ± 10.1 MR = 29.2	23.1 ± 9.4 MR = 32.3	0.55[a]	21.1 ± 8.5 MR = 28.5	23.4 ± 11.0 MR = 32.1	0.52[a]	21.14 ± 8.46 MR = 24.6	0.67[a]
Location of tremor			0.74			0.20		0.09
Upper limb (UL)	39 (83%)	13 (86.7%)		27 (90.0%)	25 (78.1%)		12 (70.6%)	
UL and cranial tremor	8 (17%)	2 (13.3%)		3 (10.0%)	7 (21.9%)		5 (29.4%)	
Family history of ET			0.46			0.89		0.53
Yes	33 (70.2%)	12 (80.0)		22 (73.3%)	23 (71.9%)		11 (35.3%)	
No	14 (29.8%)	3 (20.0%)		8 (26.7%)	9 (28.1%)		6 (64.7%)	
BDI score	8.0 ± 4.4	25.4 ± 5.9	< 0.001[b]	6.9 ± 4.4	17.2 ± 9.2	< 0.001[b]	9.9 ± 3.8	0.02[b]
BAI score	13.4 ± 7.9	27.3 ± 7.7	< 0.001[b]	8.5 ± 3.7 MR = 15.5	24.4 ± 7.1 MR = 46.5	< 0.001[a]	21.9 ± 5.7	< 0.001[b]

Chi square test was used for categorical variables.
MR = mean rank, Group D1 = patients without depressive symptoms, Group D2 = patients with depressive symptoms, Group A1 = patients without anxiety symptoms, Group A2 = patients with anxiety symptoms, Group A3 = patients with anxiety symptoms and without depressive symptoms.
[a] Mann Whitney *U* test.
[b] Independent sample *t*-test.

patients had only upper limb tremor while the remainder had upper limb tremor and additional cranial tremors.

3.2. Depression and anxiety symptoms

The mean BDI score was 12.2 ± 8.9 (n = 62). Subjects were divided into two groups according to their depressive symptom levels: those with minimal and mild depressive symptoms were Group D1 ("non-depressed") (n = 47, BDI = 8.0 ± 4.4), and those who had moderate or severe depressive symptoms were Group D2 ("depressed") (n = 15, BDI = 25.4 ± 5.9). All patients in Group D2 also had moderate or severe anxiety symptoms.

The mean BAI score was 16.7 ± 9.8. Subjects were also divided into two groups: those with minimal and mild anxiety symptoms were Group A1 (n = 30, BAI = 8.5 ± 3.7), and those with moderate or severe anxiety symptoms were Group A2 (n = 32, BAI = 24.4 ± 7.1) ($p < 0.001$). After excluding patients with depressive symptoms (i.e., Group D2) from Group A2, we created another group of patients with pure anxiety (Group A3). Table 2 shows the demographic and clinical features of each group.

3.3. Comparison of DTImetrics

3.3.1. Group D1 vs. Group D2

Right anterior thalamic radiation FA (p = 0.03); left anterior thalamic radiation FA (p = 0.04); right stria terminalis ADC (p = 0.007), MD (p = 0.006), AD (p = 0.004), RD (p = 0.03); left stria terminalis AD (p = 0.01); left amygdala FA (p = 0.003), RD (p = 0.04); right hippocampus ADC (p = 0.02) and left caudate ADC (p = 0.02), MD (p = 0.003), AD (p = 0.03) values were significantly different between Groups D1 and D2 (Table 3).

3.3.2. Group A1 vs. Group A2

Right superior cerebellar peduncle FA (p = 0.04); left amygdala FA (p = 0.05), RD (p = 0.04); right insula ADC (p = 0.05); left VLPFC FA (p = 0.05); right posterior cingulate cortex ADC (p = 0.05); and right stria terminalis ADC (p = 0.02), MD (p = 0.02) values were significantly different between A1 and A2. Left precuneus FA values were also lower in A2 group but did not reach significant level (p = 0.06) (Table 3).

3.3.3. Group A1 vs. Group A3

Left VLPFC FA (p = 0.02); left precuneus FA (0.02), right superior cerebellar peduncle FA (p = 0.05), AD (p = 0.03) differed between Group A1 and Group A3.

3.4. Correlations between DTI metrics and symptoms of anxiety and depression

There was negative correlation between BDI scores and left amygdala FA (Spearman's r = −0.32, p = 0.016) (Fig. 2) and a positive correlation between BDI score and left amygdala RD (r = 0.91, p = 0.03). BDI scores and right hippocampus ADC values were correlated (p = 0.06) but did not reach out significant level. Correlations were not significant for other brain regions that differed between Groups D1 and D2 ($p > 0.05$).

Although there was no relationship between age, gender and left amygdala FA values (according to Spearman correlation analysis, p = 0.92, p = 0.49), we used multiple linear regression models to evaluate the relationship between left amygdala DTI metrics and depressive symptoms. In first model, the BDI score was the dependent variable, and age, gender and left amygdala FA (b = −0.04, p = 0.008, Table 4) were independent variables. In a second model, the BDI score was the dependent variable, and age, gender and left amygdala RD were independent variables (b = 0.07, p = 0.003, Table 4). A significant association was found in each model between the DTI metrics and the BDI score.

In a series of correlation analyses, left VLPFC FA (r = 0.308, p = 0.02) (Fig. 3), right posterior cingulate cortex ADC (r = 0.27, p = 0.045), and left precuneus FA (r = −0.279, p = 0.04) (Fig. 4) were correlated with BAI scores. In a multiple linear regression model (dependent variable: BAI score, independent variables: age, gender, left VLPFC FA), there was an association between left VLPFC FA (b = 0.03, p = 0.035, Table 4) and BAI score. In similar model, an association was found between left precuneus FA (b = −0.06, p = 0.002, Table 4) and anxiety symptoms. Right posterior cingulate cortex did not significantly correlate with BAI score in a similar regression model (p = 0.069, Table 4).

Table 3
Comparison of DTI metrics.

		p value
Comparisons between Group D1 and Group D2	Right anterior thalamic radiation	
	FA	0.03[a]
	Left anterior thalamic radiation	
	FA	0.04[b]
	Right stria terminalis	
	ADC	0.007[a]
	MD	0.006[a]
	AD	0.004[a]
	RD	0.03[a]
	Left stria terminalis	
	MD	0.06[a]
	AD	0.01[b]
	Left amygdala	
	FA	0.003[a]
	AD	0.06[b]
	RD	0.04[a]
	Right hippocampus	
	ADC	0.02[a]
	Left caudate	
	ADC	0.02[a]
	MD	0.003[a]
	AD	0.03[a]
Comparisons between Group A1 and Group A2	Right superior cerebellar peduncle	
	FA	0.04[b]
	AD	0.06[a]
	Left amygdala	
	FA	0.05[a]
	RD	0.04[a]
	Right insula	
	ADC	0.05[b]
	Left ventrolateral prefrontal cortex (VLFPC)	
	FA	0.05[a]
	Right posterior cingulate cortex	
	ADC	0.05[b]
	MD	0.07[b]
	Right stria terminalis	
	ADC	0.02[a]
	MD	0.02[a]
	RD	0.06[a]
	Left precuneus	
	FA	0.06[b]
Comparisons between Group A1 and Group A3	Left VLFFC	
	FA	0.02[b]
	AD	0.07[b]
	Left precuneus	
	FA	0.02[b]
	AD	0.06[b]
	Right superior cerebellar peduncle	
	FA	0.05[b]
	AD	0.03[b]

[a] Mann Whitney *U* test.
[b] Independent sample *t*-test.

4. Discussion

We investigated the possible relationship between microstructural brain changes and depression and anxiety symptoms in ET. We found that microstructural brain changes in the prefrontal cortex and paralimbic and limbic structures (1) differed between ET patients with vs. without these symptoms and (2) correlated with these symptoms. These data suggest that these microstructural brain changes could play a role in the expression of these neuropsychiatric features. More specifically, the observation that these affective disturbances are associated with identifiable underlying brain changes suggests that they are not merely a secondary psychiatric response to disabling tremor but they may be primary features of the disease process itself. Indeed, prior work indicates that depressive symptoms in patients with ET can precede the onset of motor manifestations in ET [33]. Similarly, previous work shows that depressive symptoms are dissociated to some degree from tremor severity in patients with ET, further supporting the hypothesis that depression in ET represents more than a mere a psychological reaction to the tremor [34].

The prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, cerebellum and basal ganglia have been shown to be most relevant to depressive symptoms [35], and cortico-limbic-cerebellar connections have been shown to contribute to depressive neuropathology [36]. The amygdala has also become a focus of neuroanatomical research on depression as it is crucial to processing emotions and has close connections with other parts of the limbic system [37]. Additionally, the amygdala plays a role in both bottom-up and top-down processes of emotion formation and regulation. Dysfunctions of the amygdala and related networks are directly linked with depression, which is a disorder of emotions [38]. Previous depression neuroimaging studies using structural and functional MRI reported pathology of the amygdala [39–41], and in our study, left amygdala variations were related to more severe depressive symptoms in ET. Furthermore, the cerebellum and locus coeruleus have connections with the amygdala and have been implicated in ET pathology [42]. Therefore, it is possible that the amygdala and its connected brain regions can be affected by ET disease pathology.

Previous neuroimaging studies have identified specific brain variations associated with depression in PD [43–47] and Huntington disease (HD) [48–50], and the relationship between amygdala dysfunction and depression has been extensively investigated [51–57]. Surdhar et al. found that volumes in depressed PD patients were smaller compared to healthy controls in both the left ($p = 0.031$) and right ($p = 0.034$) amygdala [54]. Three additional studies in 2015 also suggested a relationship between amygdala and depression in PD [55–57]; notably, decreased left amygdala functional connectivity with the right cerebellum was observed in the depressed PD group [55]. In HD, reduced amygdala volumes have also been associated with depressive symptoms [58]. Depressive symptoms were also negatively correlated with bilateral hippocampal volumes [56] and caudate volumes [59] as observed in major depressive disorders [35]. In our study, we found a significant difference in hippocampus and caudate nucleus between depressive and non-depressive groups, though there were no associated correlates.

Similar to other neuropsychiatric illnesses, anxiety disorders are caused by functional defects in brain circuits that regulate fear and other emotions. Brain circuitry in the amygdala, anterior cingulate cortex, prefrontal cortex, thalamus, brainstem (particularly the locus coeruleus), hypothalamus, basal forebrain, bed nucleus of stria terminalis, and hippocampus are involved in anxiety [58]. The VLPFC is related to social anxiety disorders (SAD) [60, 61], disorders more commonly associated with ET [17,18], and social avoidance [61], a phenomenon observed in ET as a possible result of social phobia [18]. This region is also associated with negatively biased social predictions in anxious individuals [62]. In our study, increased VLPFC FA values were correlated with severe anxiety symptoms. Though decreased FA is generally attributed to white matter neurodegeneration, it is possible that the increased FA values in our study indicate abnormal white matter changes: (i) Increased FA in the cortical regions was correlated with gliosis; (ii) Increased FA may be an indicator of neuroinflammation, a possible predictor of neurodegeneration; and (iii) increased myelination, axonal structural impairment, and/or decreased axonal diameter may contribute to the higher FA [63–65]. In our study, decreased left precuneus FA values were related to severe anxiety symptoms; this structure has been implicated in avoidance behavior in social anxiety disorders [66]. Precuneus has a role in one's biased information processing of the negative self-perception and encoding the processing of anxious feelings [67]. Anxiety in PD, a neuropsychiatric feature of the disease, has been correlated to altered brain regions, including the caudate and putamen, prefrontal areas (e.g. orbitofrontal cortex and

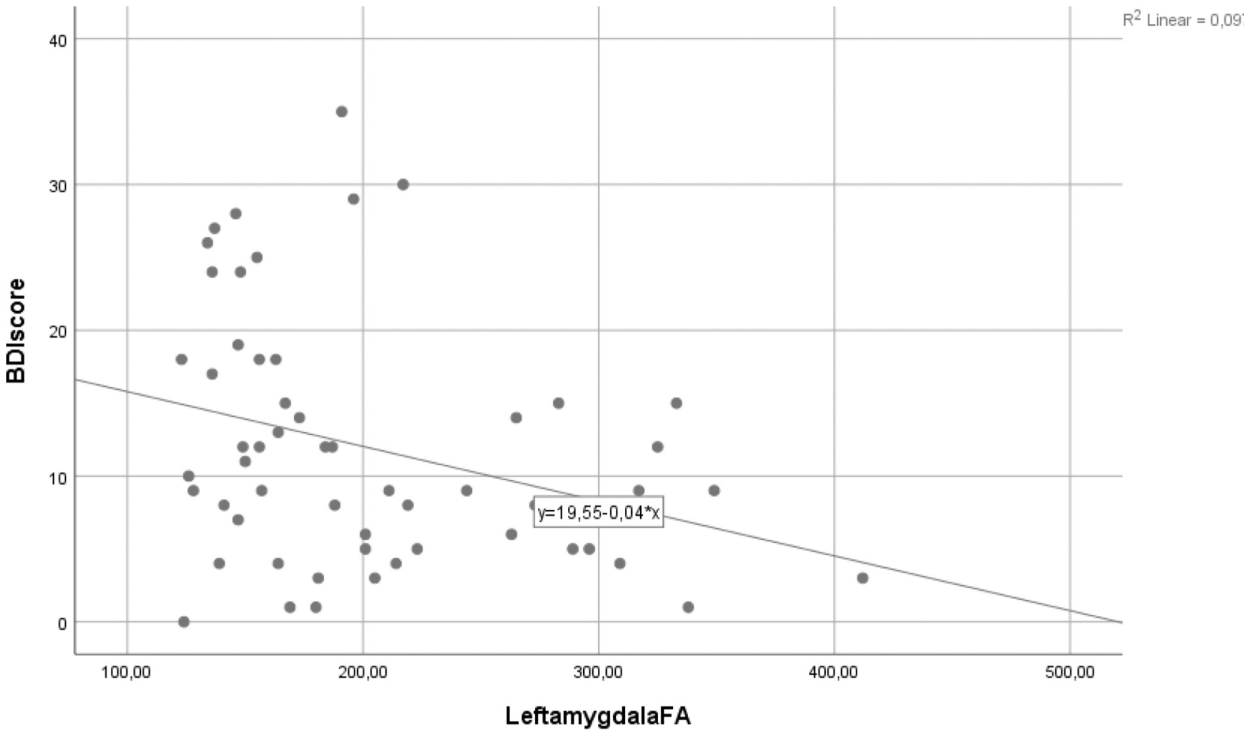

Fig. 2. Correlation between left amygdala FA values and BDI scores.

Table 4

Multiple linear regression analyses (associations between DTI metrics and severity of depressive and anxiety symptoms).

Model	*Independent variables*[a]	B	t	p value for model	p value for DTI metric[b]
Dependent variables					
Severity of depressive symptoms (BDI score)	Left amygdala FA	−0.04	−2.75	0.005	0.008
	Left amygdala RD	0.07	3.08	0.002	0.003
Severity of anxiety symptoms (BAI score)	Left VLPFC FA	0.03	2.16	0.002	0.035
	Left precuneus FA	−0.06	−3.29	< 0.001	0.002
	Right PCC[c] ADC	0.04	1.85	0.003	0.069
	Left amygdala FA	−0.03	−1.50	0.005	0.14

[a] All models include age and gender as independent variables.
[b] Multiple linear regression analysis.
[c] Posterior cingulate cortex.

inferior frontal gyrus), hippocampus, and thalamus [68], as well as the amygdala, which has been related to severe anxiety symptoms in HD [58].

This study should be assessed within the context of several limitations. All measures were based on self-report, which relies on awareness and willingness to disclose symptoms. Additionally, the number affected patients (i.e. those with higher depression or anxiety) was relatively small, but statistical tests still reached appropriate power levels. In group D2 there was a co-existence of anxiety/depression. To avoid effects of anxiety on our results of depressive patients we also compared left amygdala with BAI scores. Finally, we did not include a group of healthy normal adults and patients with depression/anxiety without ET as controls to compare with the ET and on which to examine the relationship between anxious and depressive symptoms and DTImetrics.

5. Conclusion

In our study, we found that brain microstructural changes in the amygdala were related to severe depressive symptoms in ET, and brain microstructural changes in the VLPFC and precuneus were related to severe anxiety symptoms in ET. The observation that these affective disturbances are associated with identifiable underlying brain changes suggests that they are not merely a secondary psychiatric response to disabling tremor but they may be primary features of the disease process itself. Though our study is the first to relate anxiety and depression to microstructural brain changes in ET, further work is necessary to replicate these findings.

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Declaration of Competing Interest

Authors disclose no conflicts of interest.

Financial sources

There is no financial source in this study.

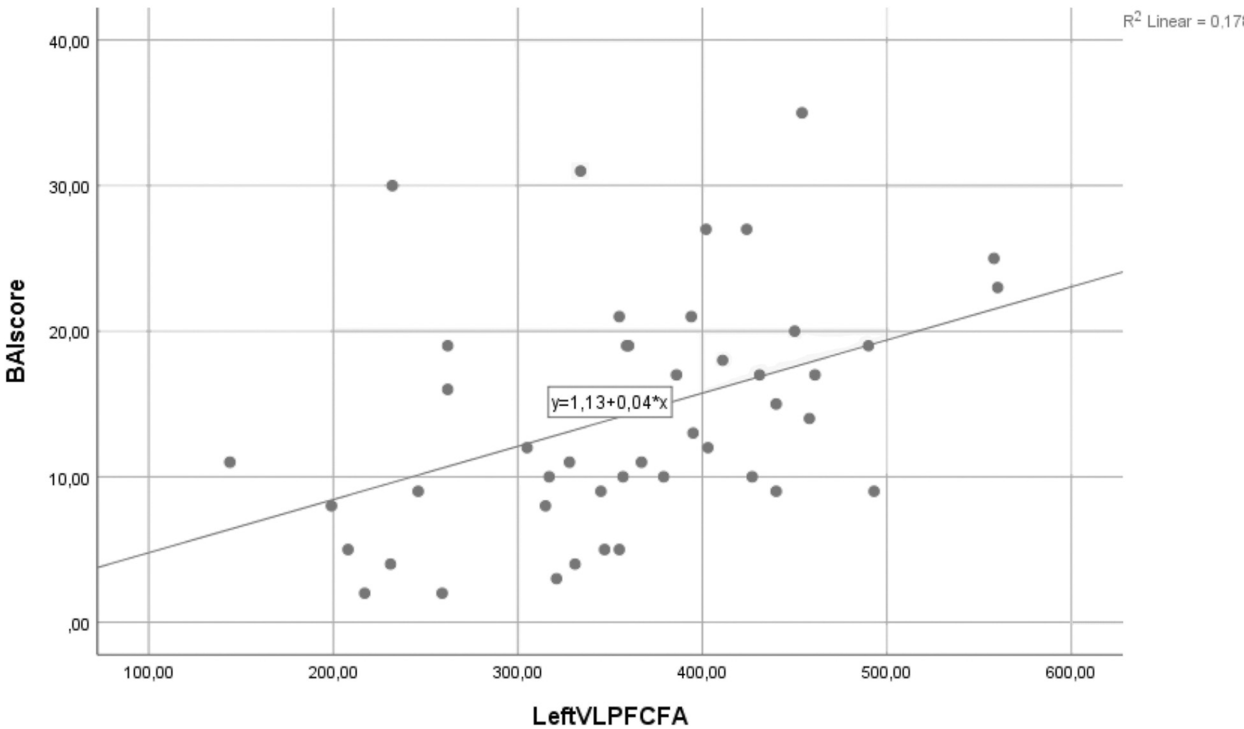

Fig. 3. Correlation between left VLPFC FA values and BAI scores.

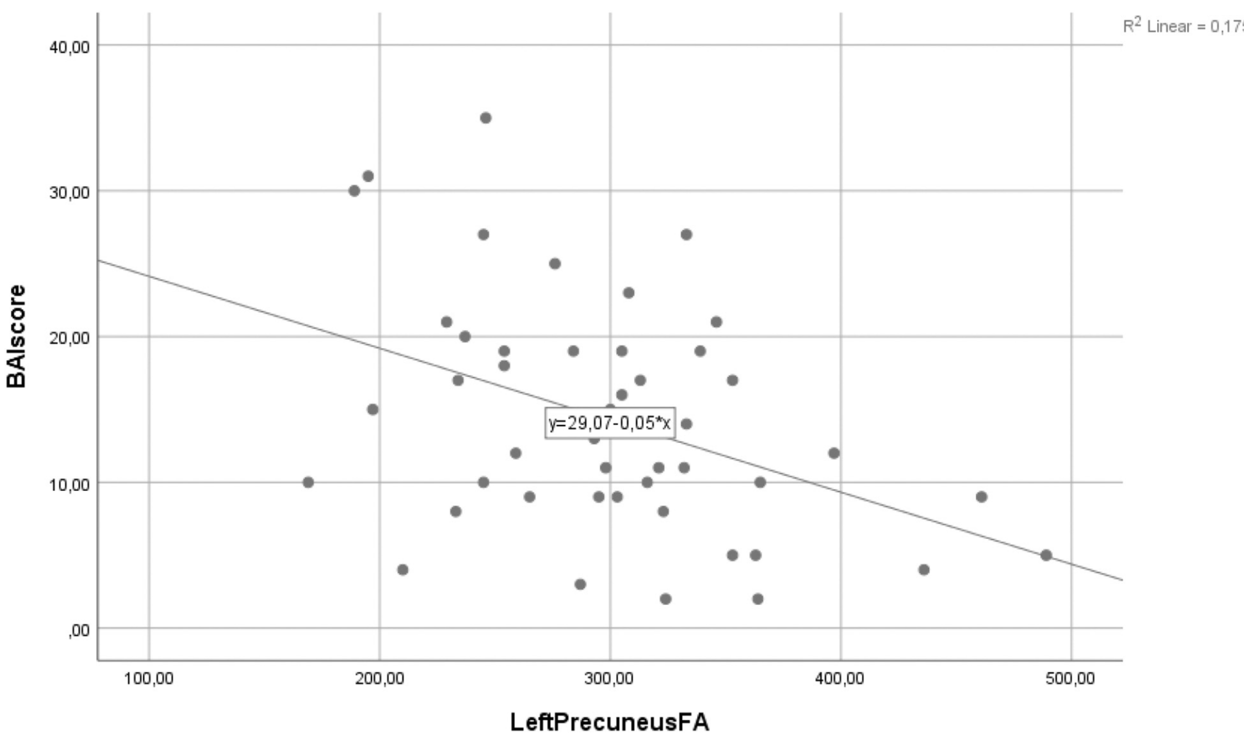

Fig. 4. Correlation between left precuneus FA values and BAI scores.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimag.2019.06.016.

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