Brain Volumetric Abnormalities, Cognitive and Psychological Profile of Patients with Conversion Neurological Symptoms

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Abstract

Background: Functional neurological disorder (FND) causes motor or sensory symptoms without a neurological cause, leading to disability and distress. Neuroimaging shows structural brain changes in regions linked to pain and emotional regulation.

Objectives: This study examines brain volumetric differences between FND patients and healthy controls, focusing on areas involved in emotion regulation and motor control.

Patients and methods: The study included 50 FND patients and 40 healthy controls. Cognitive assessments used the Trail Making Test (TMT) A and B and the Montreal Cognitive Assessment (MoCA). Brain volumetric analyses were performed using the VolBrain tool on sagittal T1-weighted MRI scans. Data were analyzed using SPSS version 24.

Results: FND patients had higher TMT-A (45.8 vs. 27.1, $p < 0.001$) and TMT-B (68.3 vs. 40.5, $p < 0.001$) scores, and lower MoCA scores (19.4 vs. 24.3, $p < 0.001$). Brain volumetry revealed decreased white matter (415.9 vs. 551.3, $p < 0.001$) and brainstem volumes (21.1 vs. 24.5, $p < 0.001$). Significant correlations were found between cognitive test scores and brain volumes.

Conclusions: Significant brain volumetric differences were found between FND patients and healthy controls, particularly in white matter and brainstem volumes. These structural abnormalities are linked to cognitive impairments in FND patients, emphasizing the need for integrated diagnostic and therapeutic approaches. Further research is needed to understand the mechanisms underlying FND.

Keywords: Functional neurological disorder; Cognitive impairment; Brain volumetry.

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Introduction

Functional neurological disorder (FND) is a condition where an individual exhibits altered motor or sensory symptoms or deficits that are not explained by another neurological or medical problem. **(Varley et al., 2023)**.The absence of identifiable neurological pathology does not diminish the severity or reality of the symptoms experienced by patients. FND accounts for about 6% of neurology outpatient visits **(Carson and Lehn, 2016)**. Comorbid neurologic illness occurs in around 10% of patients **(Carson and Lehn, 2016).** FND can manifest at any age but are most commonly diagnosed in women and young adults, with a higher prevalence in individuals exposed to significant psychological stress or trauma **(Gelauff and Stone, 2016)**.

The etiology of conversion disorders is multifactorial, involving an interplay of psychological, social, and biological factors **(Baizabal-Carvallo et al., 2019)**. Psychological theories propose that conversion symptoms may serve as a coping mechanism to manage psychological distress, converting emotional instability into physical symptoms **(Ludwig et al., 2018).** Advances in neuroimaging have shed light on the potential neurobiological causes of conversion disorders. MRI findings revealed that functional and structural brain alterations were mainly allocated in regions related with both pain perception and emotional regulation, such as the prefrontal cortex, somatosensory cortex, insula, amygdala, hippocampus, parahippocampus, and Anterior cingulate cortex **(Delvecchio et al., 2019)**.

Neuroimaging studies, particularly those utilizing brain volumetric analysis, provide valuable insights into the structural changes associated with conversion disorders. These studies have identified alterations in the volume of the white matter, limbic structures **(Zhao et al., 2018**; **DIez et al., 2021)** and other brain regions involved in motor and sensory functions.

This study aims to further explore the neurobiological underpinnings of conversion disorders by examining brain volumetric differences between patients with conversion disorders and healthy controls. We hypothesize that individuals with conversion disorders may exhibit significant differences in brain volumes, particularly in areas implicated in emotion regulation and motor control, compared to healthy controls. By integrating cognitive assessments and advanced neuroimaging techniques, this research seeks to enhance our understanding of the complex mechanisms underlying conversion disorders. Based on prior research indicating structural abnormalities in brain regions associated with emotion regulation and motor control, we hypothesize that patients with Functional Neurological Disorder (FND) will exhibit significant differences in brain volumetric measures compared to healthy controls. Specifically, we anticipate reductions in volumes of white matter, the brainstem, and other critical regions implicated in FND. The primary objectives of this study are to (1) quantify the brain volumetric differences between FND patients and healthy controls using advanced neuroimaging techniques, (2) correlate these structural differences with cognitive impairments as assessed by standardized cognitive tests, and (3) explore the potential neurobiological mechanisms underlying these findings. By achieving these objectives, we aim to contribute to a more comprehensive understanding of the neurobiological basis of FND and inform future diagnostic and therapeutic strategies.

Patients and methods

Participants

The study included 50 patients presenting with conversion neurological symptoms were diagnosed according to diagnostic criteria of DSM-5 **(APA, 2013)** and 40 healthy control subjects. Patients were recruited from the neurology outpatient clinic, and controls were selected from the general population, matched for age and sex. This study conducted during the period from April 2023 to May 2024

Study Tools

Cognitive Assessment

1. **Trail Making Test (TMT) A and B**: The Arabic validated version of the TMT was used to assess cognitive

flexibility and processing speed **(Ciolek and Lee, 2019; Stanczak et al., 2001).**

2. **Montreal Cognitive Assessment (MoCA)**: The Arabic validated version of the MoCA was utilized to screen for cognitive impairment **(Dautzenberg et al., 2020; Rahman and El Gaafary, 2009)**.

MRI Brain Volumetric Study

MRI scans were performed using a 1.5 T Philips Achieva MRI machine to acquire T1-weighted sequences. The standardized imaging parameters included an echo time (TE) of approximately 10 ms, a repetition time (TR) of around 600 ms, a slice thickness of 1 mm, a flip angle of 90 degrees, and a field of view (FOV) of approximately 240 x 240 mm. The resulting DICOM files were converted to a single NIFTI file format for uniformity and ease of analysis. These NIFTI files were then processed using the automated VolBrain pipeline, which provided detailed volumetric measurements of various brain regions. The VolBrain tool's algorithms include preprocessing steps such as brain extraction and tissue segmentation, ensuring accurate and consistent volume calculations across all subjects. This methodology allowed for precise quantification of brain volumes and comparison between FND patients and healthy controls **(Manjón and Coupé, 2016)** .

Ethical Code: All participants provided a written informed agreement, and the research was given the study's institutional ethics committee's approval at the Faculty of Medicine in Qena (SVU-MED-NAP020-1-23-3-575).

Statistical Analysis

Data were analyzed using the Statistical Program for Social Science (SPSS) version 24. Qualitative data were expressed as frequencies and percentages, while quantitative data were expressed as means and standard deviations. The following statistical tests were employed:

- **Independent sample T-test**: Used to compare mean differences between two groups.
- **Chi-square test**: Used for comparisons involving categorical data.
- **Pearson's correlation coefficient**: Used to assess the strength and direction of associations between variables.
- **P-value interpretation**:
  - P < 0.05: Considered significant.
  - P > 0.05: Considered non-significant.

Results

Demographic Data

(Table.1) presents a comparison of demographic data between patients and control groups. There were no statistically significant differences in age, sex, education, occupation, or marital status between the two groups.

Table 1. Demographic Data Comparison

Variables	Patients (N = 50)	Control (N = 40)	Stat. Test	P-value
Age (years)	31.6 ± 13.09	31.05 ± 7.5	T = 0.25	0.801
Sex (Male/Female)	19/31 (38%/62%)	14/26 (35%/65%)	$X^2 = 0.086$	0.769
Education	Primary: 15 (30%)	Primary: 9 (22.5%)	$X^2 = 3.8$	0.143
	Secondary: 31 (62%)	Secondary: 22 (55%)		
	University: 4 (8%)	University: 9 (22.5%)		
Marital Status	Single: 24 (48%)	Single: 17 (42.5%)	$X^2 = 3.5$	0.319
	Married: 19 (38%)	Married: 21 (52.5%)		
	Divorced: 5 (10%)	Divorced: 2 (5%)		
	Engaged: 2 (4%)	Engaged: 0 (0%)		

Clinical Data

The age of onset in the patient group averaged 31.1 ± 13.09 years, with a range from 13 to 60 years. The duration of symptoms varied, with most patients experiencing symptoms for days (36%) or hours (32%). Pseudo fits (22%) and speech arrest (14%) were the most common clinical manifestations, (**Table.2**).

Table 2. Clinical Data of Patients with Conversion Disorders

Clinical Variables	Patients (N = 50)
The age at onset in patient group	31.1 ± 13.09 (13 - 60)
Duration of illness	Minutes: 11 (22%)
	Hours: 16 (32%)
	Days: 18 (36%)
	Weeks: 1 (2%)
	Months: 1 (2%)
Clinical Manifestations	Right hemiplegia: 6 (12%)
	Left hemiplegia: 4 (8%)
	Paraplegia: 4 (8%)
	Right monoplegia: 0 (0%)
	Left monoplegia: 1 (2%)
	Right mouth deviation: 2 (4%)
	Left mouth deviation: 5 (10%)
	Right hemi-hypoesthesia: 1 (2%)
	Left hemi-hypoesthesia: 3 (6%)
	Speech arrest: 7 (14%)
	Pseudo fits: 11 (22%)
	Syncope: 2 (4%)
	Blepharospasm: 2 (4%)

Cognitive Assessments

The results of cognitive assessments were addressed in (**Table.3**) and showed significant differences between patients and control groups. Patients exhibited higher TMT-A and TMT-B scores, indicating slower cognitive processing speed and flexibility. Additionally, patients had lower MoCA scores, indicating greater cognitive impairment.

Table 3. Cognitive Assessments of Patients and Controls

Cognitive Test	Patients (N = 50)	Control (N = 40)	T	P-value
TMT-A (Mean ± SD)	45.8 ± 24.7 (7 - 100)	27.1 ± 10 (10 - 49)	4.5	< 0.001
TMT-B (Mean ± SD)	68.3 ± 44.8 (10 - 280)	40.5 ± 13.4 (10 - 67)	3.7	< 0.001
MoCA (Mean ± SD)	19.4 ± 4.2 (7 - 28)	24.3 ± 2.2 (19 - 28)	6.7	< 0.001

Brain Volumetry

Significant differences in brain volumetry were observed between patients and controls. Patients showed a marked decrease in white matter volume (WMV) (415.9 ± 94.5 vs. 551.3 ± 44.6, T = 8.3, P < 0.001), left hemisphere volume (515.5 ± 100.6 vs. 562.3 ± 33.1, T = 2.82, P = 0.006), and brainstem volume (21.1 ± 4.2 vs. 24.5 ± 2.4, T = 4.44, P < 0.001). Thalamus and cerebellum volumes were also significantly reduced (Thalamus: 10.4 ± 3 vs. 12.1 ± 1.1, T = 3.38, P = 0.001; Cerebellum: 126.7 ± 15.7 vs. 138.9 ± 10.9, T = 4.1, P < 0.001). Additionally, cerebellum white matter volume was lower in patients (24.1 ± 17.4 vs. 35 ± 4.9, T = 3.8, P < 0.001). These findings highlight substantial brain structural changes in patients (**Tables 4 and 5**).

Table 4. Brain Volumetry of Patients and Controls

Brain Volume	Patients (N = 50)	Control (N = 40)	T	P-value
WMV (Mean ± SD)	415.9 ± 94.5 (190.2 - 585.5)	551.3 ± 44.6 (464.8 - 638.6)	8.3	< 0.001
GMV (Mean ± SD)	766.2 ± 225.3 (497.8 - 2069.7)	722.8 ± 60.6 (613.7 - 847)	1.18	0.241
Brain WMGM (Mean ± SD)	1173.9 ± 211.9 (856.7 - 2259.9)	1230.2 ± 60 (1113.8 - 1333.4)	1.62	0.108

Cerebrum V (Mean ± SD)	1026.6 ± 204.5 (742.7 - 2123.9)	1073.5 ± 63.2 (951 - 1192.4)	1.39	0.166
Grey Matter V (Mean ± SD)	647.1 ± 215.2 (412.9 - 1948.6)	587 ± 39.2 (517.1 - 676.2)	1.74	0.085
White Matter V (Mean ± SD)	379.5 ± 78.4 (175.3 - 518.7)	486.5 ± 48.4 (405.9 - 569.9)	7.55	< 0.001
Left Hemisphere V (Mean ± SD)	515.5 ± 100.6 (365 - 1026)	562.3 ± 33.1 (498.1 - 624.6)	2.82	0.006
Brainstem V (Mean ± SD)	21.1 ± 4.2 (14.9 - 38.4)	24.5 ± 2.4 (19.9 - 29.3)	4.44	< 0.001

Table 5. Detailed Brain Volumetry of Patients and Controls

Brain Volume	**Patients (N = 50)**	**Control (N = 40)**	**T**	**P-value**
Thalamus V (Mean ± SD)	10.4 ± 3 (5.4 - 23.2)	12.1 ± 1.1 (9.5 - 14.2)	3.38	0.001
Caudate V (Mean ± SD)	7.4 ± 2.1 (4.6 - 16.9)	7.3 ± 0.9 (5.6 - 8.8)	0.28	0.778
Amygdala V (Mean ± SD)	1.59 ± 0.69 (0.45 - 3.71)	1.56 ± 0.32 (0.8 - 2.17)	0.29	0.769
Putamen V (Mean ± SD)	7.6 ± 2.3 (5.03 - 20.09)	7.1 ± 0.9 (5.53 - 8.78)	1.2	0.231
Cerebellum V (Mean ± SD)	126.7 ± 15.7 (97.3 - 155.1)	138.9 ± 10.9 (116.2 - 164.1)	4.1	< 0.001
Cerebellum GMV (Mean ± SD)	102.7 ± 18.9 (67.5 - 153.2)	103.9 ± 10.2 (86.7 - 131.1)	0.37	0.710
Cerebellum WMV (Mean ± SD)	24.1 ± 17.4 (0.03 - 64.79)	35 ± 4.9 (26.22 - 46.2)	3.8	< 0.001
Right Cerebellum V (Mean ± SD)	61.9 ± 8.4 (33 - 79)	59.9 ± 6.3 (33 - 71.3)	1.26	0.210
Left Cerebellum V (Mean ± SD)	63.7 ± 10.6 (33 - 87.6)	77.6 ± 9.4 (33 - 92.7)	6.5	< 0.001

(**Table.6**) displays the correlations between cognitive test scores (TMT-A, TMT-B, and MoCA) and various brain volumes measured in the study. Notably, significant negative correlations were observed between TMT scores and grey matter volume (GMV) and cerebrum volume, suggesting that greater volumes in these brain regions are associated with better cognitive performance. The positive correlations between MoCA scores and several brain volumes, such as the left hemisphere volume, highlight the relationship between structural brain integrity and overall cognitive function.

Table 6. Correlations between Cognitive Assessments and Brain Volumetry

Variables	**TMT-A**		**TMT-B**		**MOCA**	
	r	**p-value**	**r**	**p-value**	**r**	**p-value**
WMV	0.13	0.355	0.09	0.517	0.02	0.887
GMV	-0.25	0.076	-0.32*	0.023	0.31*	0.026
Brain WMGM	-0.25	0.75	-0.3*	0.032	0.33*	0.018
Cerebrum V	-0.36*	0.01	-0.28*	0.042	0.33*	0.019
Grey matter V	-0.39*	0.005	-0.32*	0.019	0.29*	0.039
White V	0.14	0.345	0.08	0.589	0.03	0.832

Right hemisphere V	-0.21	0.137	-0.25	0.075	0.34*	0.013
Left hemisphere V	-0.33*	0.019	-0.29*	0.039	0.37*	0.008
Brainstem V	0.05	0.736	0.14	0.342	-0.25	0.075
Hippo V	-0.07	0.64	-0.12	0.408	-0.15	0.313
Thalamus V	0.02	0.878	0.02	0.88	-0.26	0.067
Caudate	-0.44*	0.001	-0.43*	0.002	0.42*	0.002
Amygdala	-0.01	0.941	0.03	0.821	-0.18	0.22
Putamen V	-0.07	0.648	0.00	0.979	-0.20	0.156
Cerebellum V	0.11	0.459	0.09	0.517	-0.10	0.482
Cerebellum GMV	0.05	0.719	-0.01	0.956	-0.09	0.546
Cerebellum WMV	0.04	0.782	0.09	0.52	0.00	0.984
Rt cerebellum V	0.08	0.6	0.10	0.474	-0.11	0.453
Lt cerebellum V	0.17	0.243	0.10	0.483	-0.16	0.27

Discussion

This study targeted to investigate the neurobiological underpinnings of conversion disorders by examining brain volumetric differences between patients with conversion disorders and healthy controls. The findings reveal significant differences in specific brain volumes, providing insights into the structural abnormalities associated with conversion disorders.

The demographic data indicated no significant differences between patients and controls in terms of age, sex, education or marital status. This matching ensures that observed differences in brain volumes are not confounded by these demographic variables. The clinical data revealed a broad range of ages at onset and illness durations, reflecting the heterogeneity of conversion disorders. The common clinical manifestations such as pseudo fits, and speech arrest highlight the significant impact of conversion disorders on patients' lives. These findings are consistent with previous studies that have reported diverse clinical presentations and significant functional impairments in patients with conversion disorders **(Jungilligens et al., 2022)**

Patients with conversion disorders exhibited significantly higher TMT-A and TMT-B scores, indicating slower cognitive processing speed and flexibility. Additionally, patients had significantly lower MoCA scores, suggesting greater cognitive impairment. These findings align with previous research that indicating cognitive deficits in patients of functional neurological disorder, Individuals with motor functional neurological disorders have abnormalities in processing speed, attention, memory, language, visuospatial, and executive functioning **(Alluri et al., 2020,Espay et al., 2018**). The observed cognitive impairments may reflect underlying disruptions in brain networks involved in cognitive processing and executive function.

The brain volumetric analysis revealed significant differences between patients and controls in several brain regions. Patients exhibited decreased white matter volume (WMV) and reduced volumes in regions such as the left hemisphere and brainstem. These findings are consistent with prior neuroimaging studies that have identified structural abnormalities in conversion disorders **(Hassa et al., 2017).** White matter tracts are crucial for the efficient transmission

of information across the brain, and abnormalities in these tracts could contribute to the neurological symptoms observed in conversion disorders **(Aybek et al., 2015)**

White matter volume reductions in conversion disorder patients may reflect myelin abnormalities or axonal damage, which can disrupt neural communication and lead to the diverse symptoms observed in these patients **(Stojanovic et al., 2018)**. Executive functions are high-level cognitive processes that include skills like working memory, set shifting, and inhibition. These complex cognitive activities are enabled via connections between widely distributed cognitive networks, supported by white matter. **(Ribeiro et al., 2024)**.This study's findings of reduced WMV correlate with previous studies that have shown similar reductions in white matter integrity in patients with conversion disorders **(Espay et al., 2018)**.

The brainstem plays a critical role in regulating autonomic functions, motor control, and sensory processing. Structural abnormalities in the brainstem could potentially disrupt these functions, leading to the diverse neurological symptoms seen in conversion disorders **(Voon et al., 2010)**. Previous studies have also identified brainstem abnormalities in functional neurological disorders, suggesting a potential biomarker for diagnosis and treatment targets **(Aybek et al., 2014)**.

Although the differences in grey matter volume (GMV) between patients and controls were not statistically significant. Grey matter reductions have been reported in various studies of conversion disorders, particularly in regions involved in emotion regulation, such as the anterior cingulate cortex and insula **(Kozlowska et al., 2017, Hassa et al., 2017)**. These regions are integral to the processing of emotional and sensory information, and their dysfunction may contribute to the conversion symptoms.

The study also found significant reductions in the volume of the left hemisphere in patients with conversion disorders. Hemispheric asymmetries in brain structure have been implicated in various neuropsychiatric conditions, including conversion disorders. The left hemisphere is typically associated with language and motor functions, and structural abnormalities in this hemisphere may underlie the motor and speech symptoms frequently observed in conversion disorder patients **(Aybek et al., 2015)**.

The correlation analysis between cognitive assessments and brain volumetry revealed significant associations. For example, grey matter volume was negatively correlated with TMT-A and TMT-B scores, suggesting that greater grey matter volume is associated with better cognitive performance. Similarly, brainstem volume was positively correlated with MoCA scores, indicating that reduced brainstem volume is associated with greater cognitive impairment. These correlations underscore the relationship between structural brain abnormalities and cognitive deficits in conversion disorders. These findings are consistent with previous studies that have reported associations between brain structure and cognitive function in neuropsychiatric disorders **(Millman et al., 2024; Perez et al., 2018).**

Our study has several limitations that warrant consideration. Firstly, the sample size, while reasonable, may limit the generalizability of our findings. Future studies should aim for a larger and more diverse cohort to confirm and extend these results. Additionally, the potential influence of confounding factors, such as variations in symptom severity, duration of illness, and the presence of comorbid psychological conditions, should be acknowledged. These factors could potentially impact both cognitive assessments and brain volumetric measures.
Furthermore, the cross-sectional design of our study precludes the ability to draw causal inferences or observe changes over time. Longitudinal data would provide valuable insights into the progression and potential reversibility of the observed brain volumetric abnormalities. We also lacked detailed information on the participants' psychological history, which could have provided additional context for interpreting the findings.

Our findings suggest that neuroimaging could play a crucial role in the diagnostic process for FND, potentially serving as an objective tool to identify structural brain abnormalities associated with the disorder. Recognizing these abnormalities could assist in differentiating FND from other neurological conditions, thereby enhancing diagnostic accuracy. Additionally, understanding the structural underpinnings of FND may inform treatment planning, particularly in developing targeted interventions that address the specific brain regions implicated.

To build on our findings, we recommend several avenues for future research. Studies with larger sample sizes and more diverse populations are necessary to validate our results and enhance their applicability across different demographic groups. Longitudinal studies would be particularly valuable in elucidating the temporal aspects of brain changes in FND patients and assessing the impact of therapeutic interventions. Moreover, intervention studies that explore the effectiveness of various treatments, such as cognitive-behavioral therapy or pharmacological approaches, in mitigating structural brain abnormalities and improving clinical outcomes should be pursued.

Conclusion

This study provides evidence of significant differences in brain volumes between patients with conversion disorders and healthy controls. These findings contribute to our understanding of the neurobiological basis of conversion disorders and underscore the need for comprehensive approaches to diagnosis and treatment that integrate both psychological and neurobiological perspectives. Future research should continue to investigate the complex mechanisms underlying conversion disorders to improve diagnosis, treatment, and patient outcomes.

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