

Structural and Functional Neuroimaging Findings in Delusional Disorder: Diagnostic and Therapeutic Implications

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Abstract: *Background:* Although structural and functional abnormalities have been found in patients with schizophrenia, very few studies have investigated neuroimaging features in delusional disorder patients. We conducted a review of the literature to assess the evidence for specific neuroimaging changes in delusional disorder on brain structures and functions.

Method: We reviewed the literature on structural and functional neuroimaging studies of delusional disorder between 1980 and April 2014. The search was conducted through MEDLINE, Pubmed and Web of Knowledge, using the following key words: delusional disorder, neuroimaging, brain imaging, magnetic resonance, MRI, computerized tomography, TC, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET and spectroscopy.

Results: According to our inclusion criteria, 15 studies were included in the review. 14 studies reported structural brain data, and 10 studies reported functional findings. Due to the heterogeneity of the neuroimaging techniques, a meta-analysis could not be conducted. The vast majority of structural neuroimaging studies found brain atrophy and white matter lesions in DD patients, particularly in the temporoparietal or frontal lobes. Functional neuroimaging studies pointed to the temporal and parietal lobes, as well as the basal ganglia, as potential brain areas implicated in the clinical manifestation of DD, particularly in those patients affected with the somatic type, and as potential neuroimaging markers of clinical response in these populations.

Conclusion: Temporo-parietal, prefrontal, and basal ganglia dysfunction, as well as dysfunctions in other specific brain regions, may be implicated in the core symptoms of delusional patients. More complex functional brain network analyses and multivariate statistics would provide higher evidence in future research.

Keywords: Brain changes, brain imaging, delusional disorder, neuroimaging, paranoia.

INTRODUCTION

In recent years, neuroimaging studies have revealed that schizophrenia is characterized by structural [1-3] and functional focal abnormalities [4, 5].

A recent meta-analysis found grey matter reduction and volume reductions in the caudate nucleus and thalamus in over 18,000 subjects diagnosed with schizophrenia [3], and the brain loss is thought to be associated with neurodevelopmental processes and disease progression. Further, Ahmed and colleagues highlighted that neuroimaging has linked the neurotoxic and neuroprotective effects of antipsychotics with brain abnormalities in the clinical management of schizophrenia patients [2]. Additionally, structural neuroimaging has supported the notion that multiple brain circuits are impaired in these patients, and

focal abnormalities might not explain the heterogeneity of phenotypes in schizophrenia patients [1].

On the other hand, increasing evidence is available regarding the predictive value of neuroimaging in the development of psychosis within high-risk subjects, particularly for abnormalities in prefrontal, anterior cingulate, and medial temporal areas [6, 7]. However, these studies should be replicated and include larger studies with greater sample sizes.

When focusing on functional neuroimaging studies, a meta-analysis concluded that, although the dualism between hypofrontality and hyperfrontality in explaining cognitive deficits is not yet resolved, the reliability of functional neuroimaging studies has been confirmed [5]. Similarly, a recent review suggested that the combination of diffusion tensor imaging and functional neuroimaging studies would provide new data regarding the dysconnectivity theory of schizophrenia [4].

In spite of the extensive evidence in schizophrenia patients, few studies have focused on delusional disorder

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(DD) patients, and no reviews have summarized findings from structural and functional neuroimaging studies regarding these populations.

Therefore, we aimed to review the literature to assess the evidence for specific neuroimaging changes in DD on brain structures and functions.

METHOD

Search Strategy

We searched for studies reporting structural and functional neuroimaging findings in patients diagnosed with DD. We performed electronic searches through MEDLINE, Pubmed and Web of Knowledge databases from January 1980 to April 2014 using the following keywords: delusional disorder, neuroimaging, brain imaging, magnetic resonance, MRI, computerized tomography, TC, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, and spectroscopy.

Selection Criteria

Studies were included in this review if they met our inclusion criteria: (1) diagnosis of DD according to the Diagnostic and Statistic Manual of Mental Disorders DSM-III-TR, DSM-IV, or ICD-10 criteria, (2) being an original research study in a peer-reviewed journal, (2) reporting basic sociodemographic and clinical data on DD patients, and (3) showing positive or negative data on structural and/or functional neuroimaging techniques in DD. Studies that did not report DSM-III-R, DSM-IV, or ICD-10 criteria, as well as those that contained organic delusional disorder cases, were excluded.

Restrictions on publication type or design of the study were not applied, and all relevant papers in English, German, and Spanish were included. Furthermore, all relevant abstracts and references related to the aforementioned search terms were obtained and examined to identify potential additional studies.

RESULTS

Identified Studies

Our findings using the search terms previously mentioned and the number of studies included according to the inclusion criteria are described as follows:

“Delusional disorder and neuroimaging”: 114 journal articles were found. Seven articles were identified as containing data on neuroimaging in DD patients. After analysing these studies, three studies were excluded for two reasons: (1) DSM-III-R or DSM-IV diagnostic criteria were not specified in one case [8], and (2) organic DD was diagnosed in patients [9, 10].

“Delusional disorder and brain imaging”: 241 articles were found, with thirteen articles containing data on neuroimaging in DD. From the identified articles, seven studies were selected, and six studies were excluded due to several reasons: (1) one study was based on a neurological patient who was diagnosed as having organic DD [11], (2)

three studies reported findings in patients diagnosed with DD after suffering from an ischaemic cerebrovascular disease [10, 12, 13], and (3) two studies failed to report diagnostic criteria for primary DD [14, 15].

“Delusional disorder and magnetic resonance”: 175 journal articles were found in a first search performance, from which eighteen were identified. Seven works fulfilled our inclusion criteria. Six studies were excluded because they reported findings in organic DD patients [10-12, 16-18]. Further, five studies were excluded due to the following reasons: (1) no diagnostic criteria (DSM-III-R, DSM-IV) for DD were specified [8, 14, 15, 19, 20], and (2) no neuroimaging findings were reported [20].

“Delusional disorder and MRI”: 180 journal articles were found, from which twenty were identified as potentially reporting MRI findings in DD. Ten journal articles fulfilled our inclusion criteria. Studies that were not included and the reasons for exclusion are as follows: (1) five studies reported diagnostic criteria for organic DD [11, 12, 16-18], (2) one article was based on a review [21], and (3) four studies failed to report DSM-III-R or DSM-IV diagnostic criteria [8, 19, 22, 23].

“Delusional disorder and computerised tomography”: 75 studies were found, from which one was identified as being relevant. This journal article was excluded because a case of organic DD was reported [13].

“Delusional disorder and CT”: 82 journal articles can be found, from which three potentially focused on DD patients. These three articles were excluded due to several reasons: (1) one article was written in Croatian [24], (2) one article in Polish [25], and (3) the third article failed to reported diagnostic criteria for DD [26].

“Delusional disorder and single photon emission tomography”: 40 journal articles were found, from which 8 were identified as relevant to our review. From these studies, six articles were selected, and two articles were excluded because patients were diagnosed as having an organic DD [12, 18].

“Delusional disorder and SPECT”: 42 studies were found. Ten studies were identified as containing SPECT data on DD patients, and 8 studies were selected. Two journal articles were rejected as the samples contained organic DD [12, 18].

“Delusional disorder and functional magnetic resonance”: 64 journal articles were found. Four articles were identified, from which one article was excluded because a case of a DD after an ischaemic cerebrovascular disease was reported [13].

“Delusional disorder and fMRI”: 172 studies were found through this search strategy, 21 studies were identified as potentially containing fMRI data on DD patients, and 8 studies were selected for inclusion in the review. Several

journal articles were excluded due to the following reasons: (1) failing to report DD criteria according to DSM-III-R or DSM-IV [14, 22, 23, 27], (2) presenting organic DD cases [10-13, 16-18, 28], and (3) reporting no neuroimaging findings [20].

“Delusional disorder and positron emission tomography”: 32 studies were found; however, only one of these studies met our inclusion criteria.

“Delusional disorder and PET: 35 articles were found, and 2 were identified as containing PET data on DD patients, from which one article was excluded because no standardized diagnostic criteria was reported [8].

“Delusional disorder and spectroscopy”: 72 journal studies were found, but none of them reported cases of primary DD.

A total of 15 journal articles were included, whereas 14 studies reported structural neuroimaging findings, and 10 studies were focused on functional brain imaging. Statistical analysis could not be conducted due to the heterogeneity of the neuroimaging techniques that were used in these studies.

The main demographic and clinical characteristics, as well as the neuroimaging findings, of the reviewed studies can be found in Tables 1 and 2.

Structural Neuroimaging Studies

In a prospective study on 27 patients diagnosed with late-onset psychosis, Miller and co-workers [29] investigated structural brain lesions in 5 patients using computerised tomography (CT). Three of the elderly patients fulfilled the DSM-III-R criteria for DD, one patient met the criteria for schizophrenia, and one patient was diagnosed as having a manic episode with psychotic features. All DD patients had multiple subcortical white-matter lesions. In the first case, CT showed diffuse cerebral atrophy with lacunar infarcts. In the second and third cases, several lacunar infarcts were found in the basal ganglia. These three patients did not respond to pharmacological treatment.

In a study carried out by Howard *et al.* [30], fifty elderly paraphrenics and 35 healthy controls underwent structural brain magnetic resonance imaging (MRI) in a coronal plane. Of the total sample, neuroimaging findings were described in 16 DD patients. The authors reported that the volume of the left lateral ventricle was greater than the right ventricle in DD patients compared to schizophrenia patients and healthy controls. Moreover, third ventricles were larger in DD patients than the other groups.

The case of a woman suffering from a DD, somatic type, was reported by Wada and co-workers [31]. Diffuse cortical atrophy with predominance in the bilateral frontal lobes was found in MRI, in addition to multiple bilateral white matter lesions that the authors considered normal, according to the age of the patient.

On the other hand, a case of a DDST man was reported by Ota and co-workers [32]. The authors reported no structural neuroimaging findings in the MRI before and after treatment with modified electroconvulsive therapy.

Hayashi and colleagues [33] reported the case of a 77-year-old housewife, who was admitted to a psychiatric ward. The patient was given 10 mg/day of paroxetine for 7 days, and the dosage was increased to 20 mg/day after 8 days of treatment. MRI on day 17 revealed multiple bilateral lacunar infarcts in the deep white matter.

Along these lines, brain magnetic resonance imaging revealed white matter lesions on the right temporoparietal regions and atrophy of the frontal lobe in a DD, somatic type patient [34].

Nine patients diagnosed with delusional parasitosis were assessed by cranial MRI in a study carried out by Huber *et al.* [35]. Of the total sample, only one patient met diagnostic criteria for DD, primary form, who presented with generalized brain atrophy without focal cortical white matter and basal ganglia lesions.

In contrast, no structural brain abnormalities were found by Akahane and co-workers [36] in the case of a man suffering from DD, somatic type, who was successfully treated with risperidone 2-3 mg/day.

Freudenmann and colleagues [37] carried out a case-control study on neuroimaging findings in delusional infestation (DI). Two patients were diagnosed as having a DI: the first patient had the somatic type of DD, and the second patient was diagnosed with DI secondary to mild vascular encephalopathy. These patients were compared to seven healthy controls. No structural brain abnormalities were found with MRI in the primary DD patient.

A case of a 42-year-old woman diagnosed with DD, somatic type, was reported by Hayashi *et al.* [38], and her MRI revealed no structural brain abnormalities on the first admission. At her first psychiatric contact and after recovery, a SPECT analysis using technetium-ethyl cysteinate dimer was also performed.

Uezato *et al.* [39] reported the case of a DD, somatic type, successfully treated with modified electroconvulsive therapy. The authors did not find structural brain abnormalities.

Along these lines, Umezaki *et al.* [40] found no structural brain abnormalities in 8 patients diagnosed with DD, somatic type.

Wolf and colleagues [41] carried out a structural MRI study and voxel-based morphometry in 16 patients suffering from delusional infestation and compared the patients with 16 healthy controls. From the 16 cases, 6 patients were diagnosed with DD, somatic type, according to DMS-IV-TR criteria. Although neuroimaging findings were not presented using primary or secondary delusional infestation categories, patients showed lower grey matter volume than controls in the following regions: frontal, temporal, right caudate and putamen, left thalamus, and other grey matter regions. When analysing white matter volumes, patients showed higher volumes in several areas, such as the right middle cingulate and bilateral striatum, even after adjustment for the illness duration. The authors concluded that the aforementioned areas were common in both groups of patients affected by a delusional parasitosis, those patients diagnosed with primary DD and those patients suffering from a secondary delusional parasitosis. Further, the same authors [42] conducted a source-based morphometry study to investigate structural brain abnormalities in delusional infestation patients by dividing the groups according to illness aetiology. The final sample comprised 16 cases, with 6 DD patients, 3 patients exhibiting diagnostic criteria for psychotic depression, and

Table 1. Structural neuroimaging studies on delusional disorder (n=14).

Authors and Year of Publication	Study Design	Imaging Method	DD Sample Size (n)	Sample Size Comparison Group (n)	Age	DD Type	Main Findings
Miller <i>et al.</i> , 1989 [29]	Prospective	CT	3	Schizophrenia (n=1) Bipolar disorder (n=1)	Case 1: 86 Case 2: 72 Case 3: 62	Case 1: Persecutory Case 2: Persecutory Case 3: Persecutory	Case 1. <i>CT</i> : diffuse cerebral atrophy, scattered lacunar infarcts and diminished attenuation in deep white matter (frontal and parietal cortex). Case 2. <i>CT</i> : multiple subcortical white-matter lesions and lacunar infarcts in basal ganglia. Case 3. <i>CT</i> : multiple lacunar infarcts in white-matter and basal ganglia.
Howard <i>et al.</i> 1994 [30]	Cross-sectional	MRI	16	Schizophrenia (n=31) Controls (n=33)	83.19 (mean)	NA	<i>MRI</i> : right and left lateral ventricle volumes in delusional disorder were greater than those of patients with schizophrenia or healthy controls (p=0.015; p=0.006).
Wada <i>et al.</i> 1999 [31]	Case report	MRI	1	0	78	Somatic (hypochondriac)	<i>During treatment with clomipramine (41st day)</i> : mild diffuse cortical atrophy mainly in bilateral frontal lobes. Multiple small infarctions in the bilateral white matter.
Ota <i>et al.</i> 2003 [32]	Case report	MRI MRA	1	0	72	Somatic (hypochondriac)	<i>MRI</i> : no atrophy or focal lesions. <i>MRA</i> : no abnormalities.
Hayashi <i>et al.</i> 2004 [33]	Case report	MRI	1	0	77	Somatic (hypochondriac)	<i>MRI</i> : multiple small infarctions in the bilateral white matter.
Narumoto <i>et al.</i> , 2006 [34]	Case report	MRI	1	0	82	Somatic (parasitosis)	<i>MRI</i> : ventricular increased volumes, atrophy of the frontal lobe and right temporoparietal white matter lesion.
Huber <i>et al.</i> 2008 [35]	Consecutive case-series	MRI (T1, T2, FLAIR)	1	Medical secondary DP (n=5) Psychiatric secondary DP (n=3)	75	Somatic (parasitosis) 1; (100)	<i>DD</i> : slight atrophy. No focal lesions.
Akahane <i>et al.</i> , 2009 [36]	Case report	-	1	0	54	Somatic (hypochondriac)	No structural brain abnormalities.
Freudenmann <i>et al.</i> , 2010 [37]	Prospective	MRI	1	Medical secondary DP (n=1)	27	Somatic (parasitosis)	<i>MRI</i> : unremarkable.
Hayashi <i>et al.</i> , 2010 [38]	Case report	MRI	1	0	42	Somatic (oils and foul odour)	<i>MRI</i> : unremarkable.
Uezato <i>et al.</i> , 2012 [39]	Case report	MRI	1	0	53	Somatic (oral)	No structural brain abnormalities.
Umezaki <i>et al.</i> , 2013 [40]	Case series	MRI	8	8	-	Somatic (oral)	No structural brain abnormalities.
Wolf <i>et al.</i> , 2013 [41]	Cross-sectional	MRI, voxel-based morphometry	6 (from 16 DP)	16 controls	-	Somatic (parasitosis)	Lower grey matter volumes in patients in frontal, temporal areas, right striatum and left thalamus. Higher white matter volumes in bilateral striatum.
Wolf <i>et al.</i> , 2014 [42]	Cross-sectional	Source based morphometry (MRI)	6 (from 16 DP)	16 controls	-	Somatic (parasitosis)	Lower grey matter volumes in temporal and prefrontal areas, and thalamus and parietal regions. No white matter abnormalities.

Abbreviations: CT: Computerised Tomography, DD: Delusional Disorder, DP: Delusional Parasitosis, FLAIR: Fluid Attenuated Inversion Recovery, HC: Healthy Controls, LOPP: Late-Onset Paranoid Psychosis, LOP+: Late-Onset Psychosis with somatic delusions, LOP-: Late-Onset Psychosis without somatic delusions, MRI: Magnetic Resonance Imaging, MRA: Magnetic Resonance Angiography, NOS: Not Otherwise Specified, PSCH: Early-Onset Paranoid Schizophrenia.

Table 2. Functional neuroimaging studies on delusional disorder (n=10).

Authors and Year of Publication	Study Design	Imaging Method	Sample Size (n)	Sample Size Comparison Group (n)	Mean Age, Years (SD)	DD Type n; (%)	Main Findings
Wada <i>et al.</i> 1999 [31]	Case report	¹³³ Xe-SPECT	1	0	78	Somatic (hypochondriac)	<i>During treatment with clomipramine (19th day):</i> reduced regional cerebral blood flow in the left temporal and parietal lobes. <i>After total remission (96th day):</i> improved.
Ota <i>et al.</i> 2003 [32]	Case report	^{99m} Tc -ECD SPECT	1	0	72	Somatic (hypochondriac)	<i>Before treatment with m-ECT:</i> decreased perfusion in the left temporal and parietal lobes. <i>After treatment with m-ECT:</i> improvement of blood flow in these lobes.
Hayashi <i>et al.</i> 2004 [33]	Case report	¹³³ Xe-SPECT	1	0	77	Somatic (hypochondriac)	<i>During treatment with paroxetine (day 9):</i> reduced regional cerebral blood flow in the left temporal and parietal lobes. <i>After treatment with paroxetine (day 60):</i> normalized.
Narumoto <i>et al.</i> , 2006 [34]	Case report	¹²³ I SPECT	1	0	82	Somatic (paranosis)	<i>Before treatment with risperidone:</i> global decrease in r CBF. <i>After treatment with risperidone:</i> increase of r CBF in the bilateral basal ganglia, the bilateral frontal and left temporoparietal lobes.
Akahane <i>et al.</i> , 2009 [36]	Case report	SPECT	1	0	54	Somatic (hypochondriac)	Hypoperfusion in the temporal and parietal lobes.
Freudenmann <i>et al.</i> 2010 [37]	Prospective	¹⁸ F-6-fluorodopa-PET ¹²³ I-FP-CIT-SPECT IBZM-SPECT FDG-PET	1	1	27	Somatic (paranosis)	<i>FDOPA-PET:</i> reduced presynaptic striatal dopamine turnover right + left. <i>FP-CIT-SPECT:</i> DaT availability normal except for the left putamen. <i>IBZM-SPECT:</i> D ₂ R availability reduced in the left striatum. <i>FDG-PET:</i> before treatment with aripiprazole: left glucose metabolism > right in putamen und thalamus; after treatment: putamen unchanged, inverted metabolism in thalamus (right > left).
Hayashi <i>et al.</i> 2010 [38]	Case report	^{99m} Tc -ECD SPECT	1	0	42	Somatic (halitosis, paranosis)	<i>Before treatment with paroxetine:</i> reduced regional cerebral blood flow in the left temporal and parietal lobes. <i>After treatment with paroxetine:</i> hypoperfusion normalized.
Uezato <i>et al.</i> , 2012 [39]	Case report	SPECT	1	0	53	Somatic (oral)	Hyperperfusion in the right temporal lobe normalized after modified electroconvulsive therapy.
Umezaki <i>et al.</i> , 2013 [40]	Case series	^{99m} Tc -ECD SPECT	8	8	-	Somatic (oral)	Cerebral blood flow asymmetry in frontal and temporal areas.
Oflaz <i>et al.</i> , 2014 [43]	Case control study	fMRI	9	9	-	Persecutory (majority)	Impairment in the prefrontal, temporal and limbic brain regions during working memory performance tasks.

Abbreviations: DD: Delusional Disorder, DaT: Striatal Dopamine Transporter, D2R: D2 Receptor, fMRI: Functional Magnetic Resonance Imaging, HC: Healthy Controls, NA: Not Available, HMPAO: Hexamethylpropyleneamine Oxime, PET: Positron Emission Tomography, r CBF: Regional Cerebral Blood Flow, SPECT: Single Photon Emission Computed Tomography.

7 organic DD patients. Lower grey matter volumes were found in primary DD patients, affective patients, and those cases showing an organic DD, somatic type. However, in contrast with these findings, higher white matter volumes were detected in organic DD patients but not in primary DD cases or affective patients.

Functional Neuroimaging Studies

Wada and colleagues [31] reported a case of a woman diagnosed with DD, somatic type, who was successfully treated with clomipramine 20-100 mg/day. Before treatment, the Xe-133 SPECT analysis revealed a reduced r CBF in the left temporal and parietal lobes and a marked improvement in r CBF after the clinical remission.

Ota *et al.* [32] reported the case of a man diagnosed with DD, somatic type, who received treatment with modified electroconvulsive therapy. After treatment, an improvement of regional cerebral blood flow (r CBF) was shown in the left temporal and parietal lobes by SPECT.

SPECT using Xe-133 was performed twice in a 77-year-old woman who suffered from a hypochondriacal delusion [33]. On day 9, SPECT revealed reduced regional cerebral blood flow in the left and parietal lobes. However, after 60 days of treatment with paroxetine, no cerebral blood flow abnormalities were reported.

On the other hand, Narumoto and colleagues [34] reported the case of a man diagnosed with DD, somatic type, who received risperidone (1-2 mg/day) for at least 6 weeks, and an [¹²³I]-IMP SPECT analysis investigating regional cerebral blood flow (r CBF) was performed before and after treatment. Before treatment, the patient presented with a decrease in r CBF, which showed an increase in the bilateral frontal and left temporoparietal lobes and the bilateral basal ganglia.

Akahane and co-workers [36] reported a case of DD, somatic type. The authors highlighted an association in this population between risperidone treatment effectiveness and hypoperfusion in the temporal and parietal lobes.

Freudenmann and co-workers [37] studied dopaminergic neurotransmission and glucose metabolism in a case of primary DD, somatic type before and after treatment with aripiprazole using PET and SPECT techniques. Before receiving aripiprazole, the FDOPA-PET revealed reduced bilateral striatal dopamine transmission in the caudate and the putamen, but no signs of postsynaptic neuronal degeneration were shown in the IBZM-SPECT. On the other hand, FDG-PET showed stronger cerebral glucose metabolism in the left putamen and thalamus. After treatment with aripiprazole, IBZM-SPECT revealed no focal abnormalities in the striatum, FDG-PET showed an inversion of the left thalamic glucose metabolism to the right side, and the left-dominant glucose metabolism remained unchanged when compared to the pre-treatment FDG-PET. The authors concluded that this study provided unique evidence for the role of the fronto-striato-thalamo-parietal brain regions on the physiopathology of delusional parasitosis.

Hayashi and colleagues [38] reported the case of a woman suffering from a DD, somatic type. Before treatment with paroxetine, the ^{99m}Tc -ECD SPECT revealed reduced regional cerebral blood flow in the left temporal and parietal lobes. After treatment with paroxetine and a full recovery, the previously mentioned hypoperfusion was normalized.

Uezato *et al.* [39] reported the case of a Japanese woman affected by a treatment-resistant delusional disorder, somatic type, who was given modified electroconvulsive therapy. Before treatment, right temporal hyperperfusion was detected in SPECT images, which were normalized after 10 sessions of treatment.

Regional brain perfusion was investigated by Umezaki and colleagues [40] in eight patients suffering from oral cenessthenopathy and 8 healthy controls using SPECT. Qualitative analyses of the SPECT images revealed perfusion asymmetry in patients, particularly in the frontal,

temporal, and thalamic areas. On the other hand, quantitative analyses involving cerebral blood flow confirmed the perfusion asymmetry in frontal and temporal areas.

Oflaz *et al.* [43] carried out a case-control study in 9 DD patients and 9 healthy controls by investigating functional magnetic resonance imaging (f MRI) during cognitive assessment. The authors found that DD patients showed significant impairment in the prefrontal, temporal, and limbic brain areas during working memory performance tasks.

DISCUSSION

The vast majority of scientific literature, systematic reviews, and meta-analyses have been focused on neuroimaging findings in patients who are at risk for psychoses, patients experiencing a first-episode of psychosis, and patients with chronic schizophrenia [1, 7]. However, there is a lack of information regarding delusional disorder (DD) patients.

For this reason, we aimed to search for studies containing structural and functional neuroimaging findings in patients diagnosed with DD to provide a review on its clinical relevance and therapeutic implications.

Fourteen studies were found that reported structural neuroimaging findings in DD patients. In three cases of DD, somatic type, no structural brain findings were detected by MRI [32, 36, 37, 39]. Diffuse cerebral atrophy was found in several studies [29, 31, 35], and lateral ventricle volumes in DD patients were found to be greater than those of schizophrenia patients and healthy controls in a previous study [30]. In contrast, increased ventricular volumes were detected in one case [34]. When searching for brain areas involved in structural brain lesions in the white matter, controversial results were found. Brain lesions underlying the frontal lobe were reported in three cases [29,31], white matter lesions underlying the parietal lobe were reported in two cases [29], and white matter abnormalities of the right temporoparietal lobe were reported in one case [34]. Furthermore, a recent study [41] found lower grey matter volumes in delusional infestation patients in the frontal and temporal areas, as well as in the right striatum and left thalamus, and higher white matter volumes in patients compared to controls. Further, the same authors found these differences to be related to the illness aetiology. When the authors divided the sample into two groups (group 1: psychiatric cases and group 2: organic cases), differences in grey matter volumes remained significant in the whole psychiatric group, and higher white matter volumes were only confirmed for those patients diagnosed as having an organic delusional infestation [42].

In relationship with functional neuroimaging, 10 studies report several findings in DD patients.

Pre- and postsynaptic dopaminergic neurotransmission alterations were detected in the striatum and the left putamen in one case of DD [37], and a global decrease of regional cerebral blood flow (r CBF) was reported by Narumoto and colleagues [34].

When searching for specific neuroimaging brain areas, hypoperfusion in the temporal and parietal lobes have been described in five cases [31-33, 36, 38], right hyperperfusion

in the temporal lobe was described in one case [39], and global asymmetry involving both the frontal and temporal lobes [40]. On the other hand, prefrontal dysfunction was described in 9 DD patients after fMRI assessment [43].

Therapeutic Implications

With regard to the therapeutic implications of neuroimaging studies, particularly those with functional findings, several considerations should be mentioned.

Miller and colleagues [29] found multiple lacunar infarcts in three non-responder patients diagnosed with DD, suggesting that the presence of brain lesions might be a marker of non-response in this type of population. We consider that these findings are of special interest in several aspects, in particular, in terms of prognosis and treatment decision making in patients showing structural brain lesions, as neuroimaging findings might be useful clinical predictors of antipsychotic response.

When focusing on cerebral blood flow, several authors report a significant improvement in hypoperfusion of several brain regions after antidepressant treatment. First, Wada and coworkers [31] reported normalized blood flow in the temporal and parietal lobes after treatment with clomipramine. Similarly, Hayashi and colleagues [33, 38] highlighted the effectiveness of paroxetine in increasing a reduced cerebral blood flow in temporal and parietal brain areas in two cases of DD, somatic type.

With respect to antipsychotics, two authors provided data of the effectiveness of risperidone in ameliorating hypoperfusion in the temporal and parietal lobes and the basal ganglia [34, 36]. In agreement with these findings, Freudenmann *et al.* [37] found no abnormalities in the striatum after treatment with aripiprazole in comparison with pre-treatment SPECT techniques.

In a further step, two case reports can be found regarding the effectiveness of modified electroconvulsive therapy in decreasing hypoperfusion in DD patients [32, 39].

LIMITATIONS AND STRENGTHS

The findings presented in our review contain several methodological limitations, including the heterogeneity of neuroimaging techniques used in the research of brain changes in DD patients. This could have limited the generalization of results and the comparison of studies, and for this reason, meta-analytic methods could not be performed.

Regarding other methodological limitations, it should be noted that the vast majority of included studies had small sample sizes or were case reports, a fact that is important to improve in future studies.

However, we hope this review will encourage researchers to design neuroimaging studies and include prospective populations, as few studies have been focused on these patients. Another strength of this review is that we summarized the influence of some therapeutic approaches on the structure and function of brain areas in DD patients.

CONCLUSION

To date, no systematic reviews and meta-analyses have been conducted regarding the structural and functional neuroimaging findings in DD patients. However, in the last decades, several studies and case reports have focused on this population, particularly on those suffering from the somatic type. Although robust clinical conclusions can not be drawn from our review, we should emphasize that evidence from structural and functional imaging studies suggests that fronto-temporo-parietal areas, as well as the basal ganglia, may be regions of interest or targets to better explain the physiopathology of delusions and to study potential correlations between brain network dysfunction and the effects of antipsychotics. On the other hand, functional neuroimaging studies support the notion that serotonergic and dopaminergic transmission systems are involved in the pathophysiology in these patients, which is in line with the "serotonin-dopamine" hypothesis of schizophrenia.

FUTURE PERSPECTIVES

As we mentioned above, further research using consistent methodology is required for a better understanding of the neurobiological factors involved in delusional disorder and for a successful approach to the use of neuroimaging techniques for predicting outcomes or clinical trajectories in these patients.

Recent contributions to neuroscience have highlighted the potential utility of advanced Magnetic Resonance Imaging to identify new biomarkers and neuroimaging predictors of outcomes in neuropsychiatric disorders. In particular, these methods can be appropriately combined with volumetric/morphometric analyses of specific brain areas and with the assessment of brain network dysfunctions revealed by connectome studies. Furthermore, the application of multivariate and more complex statistics would be useful for the clarification of such heterogeneity of findings.

From our point of view, future neuroimaging studies in delusional disorder patients should focus on the analysis of complex functional brain networks using multivariate statistics. Along these lines, Schmidt and coworkers [44] found that dysfunctional brain connectivity in first-episode psychosis patients was normalized by treatment with antipsychotics, and these pharmacotherapies are a potential tool for restoring these dysfunctions in the integration of several brain regions. The same authors [45] emphasized that brain connectivity abnormalities, including dysfunctional connectivity within the fronto-parietal (FP) network, are potential targets for future research in psychosis.

Therefore, we encourage researchers to conduct neuroimaging studies with the aim of detecting neuroanatomical dysconnectivity in delusional disorder patients and to elucidate the potential correlation of these dysfunctions with a clinical response to antipsychotics. The homogeneity of techniques would lead to the possibility of conducting meta-analyses and systematic reviews with more robust findings and conclusions.

CONFLICT OF INTEREST

Prof. Miquel Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, AMGEN, Eli Lilly, Ferrer, Forum Pharmaceuticals, Gedeon, Hersill, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, and Servier. Alexandre González-Rodríguez and Oriol Molina-Andreu have received honoraria or paid-for travels from Pfizer, Janssen, Lundbeck-Otsuka and Ferrer. Rafael Penadés has received honoraria or paid-for travels from Otsuka-Lundbeck. Rosa Catalán has received honoraria or paid-for travels from Lilly, Lundbeck, Janssen, Ferrer, Pfizer and Bristol.

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