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Is Morgellons an organic disease? Structural and functional abnormalities implicated in the pathophysiology of delusional infestation

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Abstract

Little is known about the pathophysiology of delusional infestation (DI), a psychodermatologic condition in which patients have a fixed, false belief of being infested with parasites or inanimate material in their skin, despite lack of objective evidence. Because some delusional states, such as schizophrenia and psychotic state in bipolar disorder have been found to be associated with brain structural and functional abnormalities, a literature review was conducted to summarize available data on structural and functional abnormalities that are found to be associated with DI. A review of the literature found cases of brain imaging studies in patients with primary DI, as well as patients with secondary DI. Accumulating evidence from the studies reviewed suggests that dysfunction of the fronto-striato-thalamo-parietal network may explain how delusions manifest in DI and suggest that DI has an organic etiology. Abnormalities in the striato-thalamo-parietal network may cause false sensations of infestation through dysfunction in visuo-tactile regulation, whereas abnormalities in the frontal region may impair judgement. Delusional infestation patients also exhibit increased activation of brain structures implicated in itch processing. Furthermore, patients at high risk for cerebrovascular disease who present with secondary DI may benefit from brain imaging studies to rule out brain ischemic insult.

Keywords: delusional infestation, delusional parasitosis, neuroimaging, structural abnormalities, functional abnormalities, psychodermatology

Introduction

Delusional infestation (DI) or delusional parasitosis is a psychodermatologic condition in which patients have a firm, fixed belief of being infested with parasites or inanimate material in their skin. The monosymptomatic hypochondriacal delusion is typically accompanied by tactile hallucinations of formication, in which there is a sensation of crawling, stinging, or biting of the skin, without evidence of an actual infestation to explain cutaneous sensations [1]. Delusional ideation can be of both animate and inanimate objects and patients will often bring in samples of the supposed infesting material. Familiarity with the etiology, treatment, and clinical course of DI is particularly important for dermatologists because over half of these patients present to dermatologists for initial workup [2]. Although DI is classified as a primary psychogenic disorder, patients are often not agreeable to psychiatric referral as they have zero-to-minimal insight into their pathology. Therefore, it is important for dermatologists to build therapeutic

Abbreviations

alns)	anterior insula
aMCC	anterior midcingulate cortex
DI	Delusional infestation
fMRI	functional magnetic resonance imaging
GMV	gray matter volume
plns	right posterior insula
SBM	source-based morphometry
SMA	supplementary motor area
VBX	voxel-based morphometry
WMV	white matter volume

rapport to provide appropriate management of these patients.

Delusional infestation is a delusional, somatic disorder that can be classified as “primary” (i.e. occurring spontaneously; usually isolated delusion with otherwise intact psyche) or “secondary” (i.e. caused by other, broader underlying psychiatric or medical disorders or substance abuse). Typically, primary DI patients are female, older in age, and have a long duration of symptoms over many years [2]. The exact etiology of DI is unknown. Nevertheless, some delusional and psychotic states have been found to be associated with brain structural abnormalities. The claustrum has been implicated in the delusional states associated with schizophrenia [3]. The hippocampus has been implicated in the psychotic states associated with bipolar disorder [4]. The insular cortex has been associated with hallucinations [5] and delusions [6] in bipolar patients. This led to the hypothesis that there may also be structural and functional abnormalities in DI and brain imaging studies may provide some insight into the etiology of DI. This review attempts to summarize the currently available data in the worldwide literature reporting results of brain imaging studies in patients with primary and secondary DI.

Methods

The electronic databases from PubMed and PsycINFO were used to complete this literature review. The search terms “delusional infestation,” “delusional infestation MRI,” “delusional infestation imaging studies,” “delusional parasitosis,” and “Morgellons,” were queried to find peer-reviewed journal articles in April 2020. Non-research articles, letters, commentaries, and other irrelevant publications were excluded. Although an initial attempt was made to only include cases of primary DI, the literature on DI is limited and often includes results from cases of both primary and secondary DI.

For cases with brain lesions reviewed, the patient’s demographic information (age and sex) and past medical history were recorded. The brain structures implicated in cases with brain lesions of DI were

identified. Cases were separated based on the particular brain structure implicated. If a DI patient had multiple brain structures with lesions the case was included in multiple sections.

Results

A. Results from structural imaging studies

Of the limited neuroimaging studies in the literature, structural MRI studies have been the most common type of neuroimaging study for patients with DI. Finding structural differences between patients with DI and healthy controls is key to elucidating the pathophysiology of DI. We review the results of neuroimaging studies that show differences between patients with DI and controls in (1a) gray and white matter volume, (2a) cortical thickness, surface area, and folding, and (3a) brain lesions. A summary of the findings from section 1a and 2a can be found in [Table 1](#).

1a. Gray and white matter volume

Brain regions in which patients exhibit differences in gray and white matter volume can help indicate which structures and networks are implicated in DI. MRI studies using voxel-based morphometry (VBX) and source-based morphometry (SBM) found that compared to controls, patients with DI have lower gray matter volume (GMV) in frontal, temporal, parietal, insular, thalamic, and striatal areas [7,8]. The VBX technique revealed that patients with DI compared to controls had higher white matter volume (WMV) in right middle cingulate, left frontal opercular, and bilateral striatal (caudate, putamen) areas [7]. Notably, the patients categorized as DI patients were a mixture of primary DI, secondary to psychiatric depression, and secondary to medical conditions. Evaluating different categories of DI patients as one group helps increase the significance of these findings. However, this overlooks a possibility that different categories of DI may have different etiologies. The SBM technique revealed that only patients with DI secondary to medical conditions showed significantly increased WMV. No WMV changes were found to be significant between controls, patients with primary DI, and patients with secondary DI [8]. This nuance in the WMV findings

might be because the SBM method notes changes in structural networks (i.e. the relationship between multiple brain regions), whereas VBM can only note volume changes. However, abnormalities in WMV could be because all patients were already on therapy such as antipsychotics at the time of imaging. Given that it is difficult to recruit DI patients for neuroimaging studies, few studies have performed imaging on patients before and after therapy. Overall, lower GMV specifically in the fronto-striato-thalamo-parietal network seems to play a dominant role in DI pathology, whereas WMV does not seem to play as important a role as GMV.

Gray matter volume and WMV of DI patients have also been compared against patients with non-somatic delusions (i.e. delusions that are not associated with the body such as jealousy or persecution). Patients with DI are considered to have somatic delusions, delusions associated with the body. A study showed that patients with DI exhibit different patterns of GMV and WMV when compared to patients with non-somatic delusions and controls [9]. When compared to controls, patients with DI had lower GMV in fronto-striato-thalamo-parietal regions, whereas patients with non-somatic delusions only had lower GMV in the left inferior temporal cortex and right fusiform cortex. Patients with DI had lower striatal and frontotemporal network strength than patients with non-somatic delusions and controls.

Although somatosensory process and networks are typically associated with the cerebrum, the cerebellum also seems to play an important role in somatosensory processes and predictions in addition to its main role in motor integration and executive control. A recent study revealed that there are GMV changes in the cerebellum of DI patients compared to patients with non-somatic delusions, patients with schizophrenia, and controls [10]. Overall, DI patients exhibited lower GMV in sensorimotor areas of the cerebellum and exhibited higher GMV in areas of the cognition cerebellum associated with cognition and emotion. The lobules of the cerebellum can be classified into three functional domains: (1) sensorimotor function in anterior lobe (i.e. lobule I-V and lobule VIII), (2)

cognitive and affective function in posterior lobe (lobule VI-IX), and (3) transition zone (i.e. lobule VI). Comparing DI patients to controls, lower GMV was found in the left lobule VIIIa. Comparing DI patients to non-somatic patients, lower GMV was found in lobule V and higher GMV was found in bilateral lobule VIIa/crusII. Comparing patients with DI to patients with schizophrenia, lower GMV was found in lobule V, but this was not statistically significant.

2a. Cortical thickness, surface area, and folding

Cortical features such as thickness, surface area, and folding are also important for understanding the pathophysiology of DI. Cortical thickness and cortical surface area are actually preferred over GMV for understanding the evolutionary and genetic origins of disorders [11]. Cortical volume, which can be derived from the product of cortical thickness and surface area, is highly heritable. Volumetric studies, or studies that use VBM or SBM methods, provide only a gross measure of gray matter abnormalities. Given the rare prevalence of DI, there is very little research on the genetic origin of DI, so understanding cortical features of imaging is a first step toward understanding the genetic origin of DI. In a study of MRI scans of 18 patients with DI and 20 controls, surface analyses found alternations in the frontoparietal patterns of the cortical thickness, surface area, and local gyrification index of DI patients compared to controls [10]. Patients with DI had higher cortical thickness in the right medial orbitofrontal gyrus compared to controls. Patients with DI had smaller cortical area in the left inferior temporal gyrus, the left precuneus, the pars orbitalis of the right frontal gyrus, and the right lingual gyrus. Patients with DI show reduced cortical gyrification in the left precentral gyrus, the left postcentral gyrus, the right precentral gyrus, the middle temporal gyrus, the banks of the right superior temporal sulcus, the right inferior parietal gyrus, and the right superior parietal gyrus.

3a. Brain lesions

Macroscopic structural lesions in the brain may indicate pathophysiology of delusional infestation. Given the limited number of imaging studies, we have compiled an up-to-date list of cases in the literature indicating brain lesions in patients with

primary or secondary DI to identify structures of interest in DI. There are many different kinds of brain lesions found such as ischemic or gliotic lesions. There was a total of nine peer-reviewed articles and 29 cases of primary or secondary DI with available data on brain lesion imaging studies. The majority of patients studied were females of older age, mostly in the 70s and 80s. Commonly, patients had co-morbid general medical conditions such as hypertension and cerebrovascular disease.

3a.1 Lesions of the caudate nucleus

The caudate nucleus forms the dorsal striatum along with the putamen and has many motor and non-motor functions [12]. There have been ten cases of secondary DI in the literature that have reported structural lesions involving the caudate as summarized in [Table 2](#). Nine of these ten cases were related to general medical conditions and one case was a result of substance abuse. Of the ten cases, four demonstrated lesions strictly of the right caudate, three demonstrated lesions strictly of the left caudate, and three demonstrated lesions of both the left and right caudate. Of note, full or partial remission was achieved in two of these cases using risperidone, two using haloperidol, two using aripiprazole, one using olanzapine, one using ziprasidone, and one using quetiapine; one did not achieve remission despite multiple anti-psychotic therapies.

3a.2 Lesions of the putamen

The putamen is a structure in the forebrain that, along with the caudate nucleus, forms the dorsal striatum and has many motor and non-motor functions [12]. There were nine cases of DI-like symptoms in the literature that reported structural lesions involving the putamen as summarized in [Table 3](#). Eight cases were related to general medical conditions and one case was a result of substance abuse. Of the nine cases, two showed lesions strictly of the left putamen, two showed lesions strictly of the right putamen, and five showed lesions of both the left and right putamen. Of note, full or partial remission was achieved in two of these cases using risperidone, two using haloperidol, two using aripiprazole, one using olanzapine, one using ziprasidone, and one using quetiapine.

3a.3 Lesions of the centrum semiovale

The centrum semiovale is a mass of white matter located beneath the cerebral cortex that carries various nerve fibers [12]. There have been two cases of DI and six cases of DI-like symptoms in the literature that have reported structural lesions involving the centrum semiovale as summarized in [Table 4](#). Two cases were DI without any underlying cause, five cases were DI-like symptoms related to general medical conditions, and one case was owing to a pre-existing psychiatric illness. Of these cases, all included bilateral lesions of the centrum semiovale. Of note, full or partial remission was achieved in three of these cases using risperidone, one using haloperidol, one using olanzapine, one using ziprasidone, and one using quetiapine; one did not achieve remission despite multiple therapies.

3a.4 Lesions of the external capsule

The external capsule contains association fibers that connect various parts of the cortex [12]. There have been five cases of DI-like symptoms in the literature that have reported structural lesions involving the external capsule as summarized in [Table 5](#). All cases were DI-like symptoms due to general medical conditions, including hypertension, meningioma, cerebrovascular arteriosclerosis, and diabetic neuropathy. Of these cases, two showed lesions of the left external capsule, two of the right external capsule, and one of the bilateral lesions of the external capsule. Of note, full or partial remission was achieved in two cases using quetiapine, one using haloperidol, one using ziprasidone, and one using aripiprazole.

3a.5 Lesions of the thalamus

The thalamus is a structure in the forebrain that relays sensory and motor signals to the cerebral cortex [12]. There have been three cases of DI-like symptoms in the literature that have reported structural lesions involving the thalamus as summarized in [Table 6](#). All the cases were DI-like symptoms related to other conditions; two cases were associated with general medical conditions and one case was owing to substance abuse (methamphetamine, ecstasy, cannabis, and alcohol). Of these cases, all showed lesions of the left thalamus. Of note, full or partial remission was

Table 6. Cases involving thalamus.

Case	Age/ Sex	Classification	Past Medical History	Symptoms	Clinical Course	Imaging modality	Laterality	Imaging Findings
3 [25]	81/M	Secondary to general medical condition	Hypertension, treated for >30 years, COPD, cholangiocarcinoma for 1 year	Feeling and seeing flies, insects, lice biting his body and mostly the head, hands, and arms	Imaging done 7 years after onset, full remission after olanzapine 10mg daily for 9 years	MRI	Left	Small lesion
1 [36]	71/F	Secondary to general medical condition	Neurocysticercosis s/p treatment with albendazole and steroid, cognitive decline, hypertriglyceridemia, hypercholesterolemia	Feeling small animals living in her skin with sensation of pruritus	Imaging done 2 years after onset, no response after trials of sertraline 50mg daily, quetiapine 50mg daily, duloxetine 60mg daily, or risperidone 3mg daily	MRI	Left	Multiple well-delimited rounded lesions surrounded by edema
1 [13]	27/F	Secondary to substance use	Polysubstance abuse (methamphetamine up to 3g daily months and ecstasy up to 10 pills daily for 6 months, cannabis up to 8 joints daily for 4.5 years, alcohol binges)	Feeling small bugs on her skin and generalized pruritus	Imaging done 4.5 years after onset, full remission after risperidone 6mg daily with relapse after suspension of risperidone due to weight gain. Full remission after aripiprazole 10mg daily	PET, SPECT	Left	Increased glucose metabolism

achieved, in one case using olanzapine, and one using aripiprazole in the patient with substance abuse. One did not achieve remission despite multiple therapies.

B. Results from functional imaging studies

Although structural imaging studies can uncover brain damage or abnormalities in regions that are implicated in DI, functional imaging studies can show which brain areas and processes are associated with cognition and behavior. Few functional imaging studies are found in the literature. The current functional imaging studies can be found in **Table 7**. The study by Huber and colleagues in 2007 of two cases of DI (one secondary to drug use and one secondary to a medication condition) used 6 different neuroimaging techniques to investigate brain circuitry in DI and the role of postsynaptic D2 receptors [13]. This was the first study to image patients before and after the use of antipsychotic

treatment, which is notoriously difficult in DI patients. This study provides evidence for the reduced availability of the striatal dopamine transporter in the putamen and supports the hypothesis that DI is caused by dysfunction of striatal dopamine transporter [14]. In the first case reported in Huber et al. 2007, pre- and postsynaptic dopaminergic neurotransmission were altered in the striatum (mainly in the left putamen). Glucose metabolism was found to be dominant in the left thalamus and putamen. The patient achieved full remission on an antipsychotic medication, aripiprazole, when 63 to 78% striatal dopamine D2 receptor occupancy was achieved with this medication. The second case demonstrated reduced cerebral blood flow and GMV in the frontal cortex, striatum, putamen, thalamus, and different parts of parietal cortex. The patient achieved partial remission in response to ziprasidone. This functional imaging study provides further support that DI is

Table 7. Summary of functional MRI findings.

Study	Number of patients/number of controls	Method	Findings
Freudenmann RW et al. 2010 [13]	<u>2 DI patients</u> -1 Secondary to Drug Use -1 Secondary to Medical condition	-FDG-PET -FDOPA-PET -123-FP-CIT-SPECT -IBZM-SPECT -MRI-based CASL -VBM	-First study to use six imaging techniques to compare neurotransmission in patients before and after treatment with aripiprazole -In the patient with DI secondary to drug use, cerebral glucose metabolism and dopaminergic neurotransmission were studied in the untreated state (FDG-PET, FDOPA-PET, 123I-FP-CIT-SPECT, and IBZM-SPECT) and after effective aripiprazole treatment (FDG-PET and IBZM-SPECT) -In the patient with DI secondary to medical condition, cerebral perfusion and gray matter volume changes were investigated in the untreated state and compared to N = 7 age-matched healthy controls (MRI-based CASL and VBM) -Reduced availability of presynaptic Dopamine Transporter (DaT) in the left putamen supports DaT hypothesis of DI due to reduced -Effective antipsychotic treatment seems to depend on at least 63 to 78% striatal D2 receptor occupancy and glucose metabolism changes in the bilateral thalamus -Supports dysfunctional fronto-striato-thalamo-parietal network as the neural basis of DI i.e. a priori brain regions involved in judgement (frontal cortex), sensory gating (thalamus) and body perception (dorsal striatum, thalamus and somatic cortices)
Ponson et al. 2015 [15]	<u>1 DI patient</u> -1 Primary DI	-functional magnetic resonance imaging (fMRI)	-Patient showed increased activation in the supplementary motor area (SMA) before antipsychotic treatment, and normalized function in SMA after antipsychotic therapy (aripiprazole) -Improvement of delusional infestation is associated with normalization of brain activity
Eccles et al. 2015 [16]	<u>6 DI patients</u> -5 Primary DI -1 Secondary to Drug Use	-fMRI	-First MRI study to show patients with DI have altered central processing of infestation-relevant stimuli -Patients with DI showed increased activity in the amygdala, insula, middle temporal lobe, and frontal cortices compared to controls in response to infestation-relevant stimuli (e.g. insects crawling). -In response to behavioral tasks, patients with DI demonstrated less accurate perception of internal bodily state and malleability of self-representation

associated with dysfunction of the fronto-striato-thalamo-parietal network.

Another case report presents one patient with primary DI with functional magnetic resonance imaging (fMRI) before and after the administration of antipsychotic treatment [15]. The patient achieved full remission with aripiprazole. This study showed increased brain activation in the supplementary motor area (SMA) before antipsychotic treatment. After antipsychotic treatment the patient showed normalized activity in the SMA.

The largest study accomplished in functional imaging of DI compared six patients experiencing skin infestations and fifteen age/sex-matched healthy controls [16]. First, participants underwent

fMRI while viewing infestation-related stimuli. Second, participants completed two behavioral tasks that measured self-representation: interoceptive accuracy and susceptibility to the rubber hand illusion. This study demonstrated that the processing of infestation-related stimuli is different in DI patients as compared to controls as described below. Additionally, DI patients performed poorly compared to healthy controls on measures of self-representation including interoceptive accuracy, interoceptive trait prediction, and susceptibility to the rubber hand illusion. In the rubber hand illusion, patients were instructed to place their hand in a box concealed from their view. A rubber hand was placed in front of them and lined up with their right shoulder. A cloth concealed the box and the stump

of the rubber hand so the patient could only see the rubber hand but not their real hand. Both the real and rubber hands were stroked at the same time and speed for one minute and the patient was under the illusion that the rubber hand was a part of their own body. Patients with DI showed differences in neural activity within amygdala, insula, middle temporal lobe, and frontal cortices. When shown images of insects and non-insects, DI patients showed stronger activation in the right posterior insula/secondary somatosensory cortex to all stimuli pictured on skin. In contrast, controls activated this region when shown images of insect but not non-insects. DI patients also showed greater activation of amygdala and parahippocampus compared to controls. In addition, controls showed greater activation within bilateral frontal cortex than patients. DI patients showed a marked deactivation of the bilateral frontal cortices when shown insects, which suggests a deficit in a region important for cognitive control.

Discussion

In this review, we have summarized the structural and functional imaging studies to-date in patients with primary and secondary DI. Overall, the reviewed studies revealed three main points. (1) Dysfunction in the fronto-striato-thalamo-parietal network may explain how delusions manifest in DI [7,9,10]. (2) Patients with DI activate structures implicated in the neural network for itch processing [16]. (3) Ischemic changes in areas of the brain that control visuo-tactile perception may contribute to the development of secondary DI [17].

(1) Dysfunction of the fronto-striato-thalamo-parietal network

Dysfunction of the fronto-striato-thalamo parietal network is demonstrated both structurally (i.e. decreased GMV volume, smaller cortical surface area, reduced cortical gyrification, and abnormal lesions) and functionally (i.e. reduced regional cerebral blood flow) and is illustrated in **Figure 1** [7,8,13,18]. These findings support the “two-factor model of delusions,” which is a cognitive-behavioral model for understanding the neurobiological basis of delusions. The “two-factor model of delusions”

suggests that there are two factors responsible for emerging delusions [19]. The first factor is responsible for the content of delusional belief (i.e. false ideation of infestation triggered and maintained by tactile hallucinations) and the second factor is responsible for not rejecting the belief despite evidence that the belief is false [20,21]. In DI, the first factor or “content” is hallucinatory sensations of infestation and pruritus caused by abnormalities in the striato-thalamo-parietal region that disrupts bodily perception, somatosensation, and proprioception [7-10,13,22]. The second factor in DI is impaired judgement and errors in probabilistic reasoning caused by abnormalities in the frontal region of the brain [7-10,13,22].

Numerous structural and functional abnormalities in striato-thalamo-parietal regions involved in visuo-tactile regulation were reported. Patients with DI have decreased GMV in the aforementioned regions as compared to controls [7-9]. Also, patients with DI have smaller cortical surface area in lingual gyrus, which is found in primary visual cortex and associated with encoding of visual information [23], and in the precuneus, which is found in parietal cortex and responsible for integration of stimuli [24]. A reduction in cortical gyrification in the postcentral gyrus, an area found in the primary somatosensory

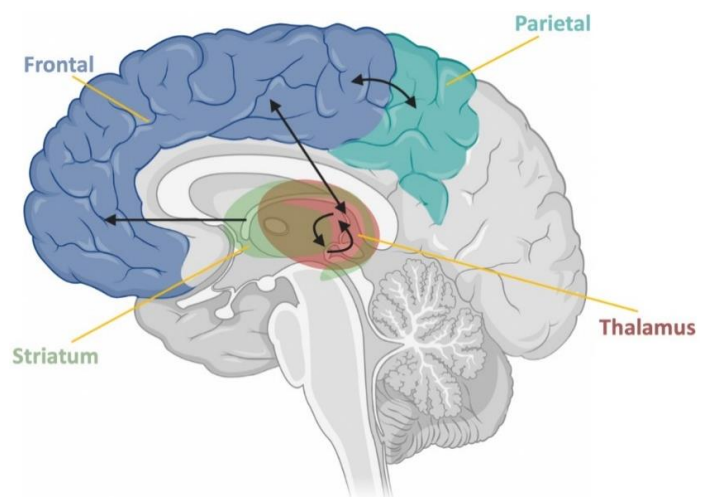


Figure 1. Fronto-striato-thalamo-parietal network. Schematic diagram illustrating the main structures implicated in the pathophysiology of delusional infestation, including the frontal lobe, striatum, thalamus, and parietal lobe. Black arrows between structures indicate connectivity between structures. Created with BioRender.com.

cortex and is involved in proprioception, thermoreception, and nociception, was also noted in DI patients [7]. A functional imaging study showed reduced availability of presynaptic dopamine transporters, especially in the putamen [13,14]. Brain lesions in the caudate nucleus, putamen, centrum semiovale, and external capsule were most commonly associated with primary DI. The caudate nucleus and putamen are forebrain structures that form the dorsal striatum and are important in tactile perception [25]. The dorsal striatum is one of the structures in the basal ganglia, which is associated with sensorimotor, cognitive, emotional, and motivational functions [26]. The centrum semiovale and external capsule carry various nerve fibers connecting different parts of the cortex. Thalamic nuclei correspond with sensory centers to receive and send sensory signals to the appropriate cortical locations in the brain. Of note, the ventral posterior nucleus of the thalamus is particularly important in sending somatosensory information such as touch and proprioception to the primary somatosensory cortex [27]. Given that these areas are all involved with visuo-tactile regulation, it is possible that abnormalities of these structures contribute to the emergence of false sensations of infestation in DI.

Structural and functional abnormalities in frontal regions involved in executive control and association were also reported. Patients with DI have decreased GMV in frontal regions as compared to controls [7,8]. Smaller cortical surface area was also reported in frontal regions such as pars orbitalis of the right frontal gyrus [18]. Reduction in surface area of this region may lead to cognitive inflexibility [28]. Notably, while viewing insects, DI patients showed a deactivation of bilateral frontal cortices, which are important for cognitive control, as compared to controls [16]. Therefore, structural abnormalities and deactivation of the frontal region implicate a potential neurobiological mechanism for the irrational, fixated nature in the belief of infestation related to disrupted cognitive control and rationality.

(2) Brain structures in delusional infestation associated with itch processing

Many structures that showed increased activation in functional imaging studies in DI are implicated in a

key brain network to process itch. The network recently identified in itch processing is between the right posterior insula and SMA, pre-SMA, anterior midcingulate cortex, anterior insula, secondary somatosensory cortex, and basal ganglia and is summarized in **Figure 2** [29]. An itch signal travels from the thalamus to the right posterior insula which has strong functional connectivity with the anterior insula, basal ganglia, and secondary somatosensory cortex. The anterior insula has strong functional connections with the pre-SMA/SMA and anterior midcingulate cortex; signals may transmit from the right posterior insula to the pre-SMA/SMA and anterior midcingulate cortex via the anterior insula [29,30]. Patients with DI exhibited greater activation of the right posterior insula and secondary somatosensory cortex to all stimuli on skin as compared to controls [16]. Notably, controls deactivated the right posterior insula and secondary somatosensory cortex when viewing non-insect images on skin, but controls activated the aforementioned regions when viewing insects. This suggests that DI patients may perceive stronger sensations of itch to a variety of stimuli on skin explaining their strong perceptions of pruritus. In addition, another functional imaging study showed increased activation of SMA before treatment with aripiprazole and decreased activation of SMA after treatment [15]. The role of SMA in the itch processing network suggests that there is abnormal activation

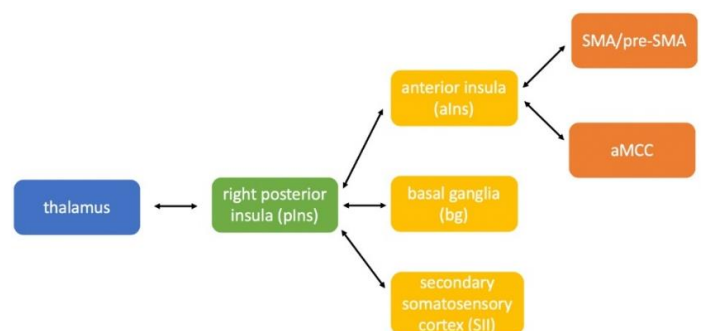


Figure 2. Functional network of itch processing. Flow chart of network believed to be important in itch processing, including the right posterior insula (plns), supplementary motor area (SMA), pre-SMA, anterior midcingulate cortex (aMCC), anterior insula (alns), secondary somatosensory cortex (SII), and basal ganglia. Arrows between structures indicate potential connectivity, but further research is still needed to confirm exact connectivity between structures.

of itch processing in untreated DI patients. Given that multiple brain structures that exhibit increased activation in DI patients are involved in the itch processing network, it is possible that DI patients experience strong pruritus related to abnormal activation of higher cortical itch processing.

(3) Brain lesions in secondary delusional infestation

Brain lesions commonly identified in patients with secondary DI were unspecified small lesions, followed by ischemic lacunar lesions and gliosis, a nonspecific reactive change of glial cells that occurs as a result of central nervous system damage or disease [17]. Cerebrovascular disorders, including cerebrovascular ischemia, are well-established as causes of secondary DI [25,31]. Secondary DI symptoms have previously been reported in association with senile dementia and cerebrovascular accidents [32], as well as hypertension [2]. The most common co-morbid medical condition found in patients with DI secondary to a general medical condition was cerebrovascular disease and hypertension. Accordingly, patients presenting with secondary DI and comorbidities of cerebrovascular disease, hypertension and cognitive decline may benefit from brain imaging as a screening modality to rule out structural lesions underlying secondary DI.

Historically, DI was described as having no underlying organic or psychiatric cause [1]. DI was only diagnosed after all other potential causes were ruled out such as schizophrenia, depression, nutritional deficiencies, thyroid disease, Parkinson disease, formication without delusion, substance abuse, and organic psychosis. However, the compiled evidence from the structural and functional imaging studies in this review demonstrate that DI has distinct biological underpinnings. In comparison, schizophrenia has also historically been considered a psychological disorder with no organic basis [33]. Accumulating evidence from neuroimaging studies identifying the structural and functional abnormalities in schizophrenia have demonstrated a distinct biological basis of schizophrenia [34,35]. Similarly, this review supports that DI has biological underpinnings related to dysfunction in the fronto-

striato-thalamo-parietal network and regions associated with itch processing.

Limitations

There are a few important limitations to highlight. Owing to the limited number of primary and secondary DI with brain imaging studies in the current literature, definitive conclusions cannot be made. The number of cases of DI was especially limited, as patients diagnosed with DI likely do not undergo brain imaging as part of current standard of care. Results from studies may be contradictory because different MRI techniques can reveal different results.

Conclusion

Although DI was previously believed to have no underlying organic etiology, the structural and functional abnormalities in patients with DI present strong evidence that there is an underlying organic cause of DI. Delusional infestation has a distinct biological basis potentially caused by dysfunction in the fronto-striato-thalamo-parietal network. Abnormalities in the striato-thalamo-parietal network may cause false perceptions of infestation and pruritus, whereas abnormalities in the frontal region may cause impaired judgement and inability to interpret false sensations. In suspected cases of DI, a full workup is recommended to rule out any underlying causes that could potentially cause DI and imaging studies may be considered to search for potential associated brain abnormalities. This may be especially valuable in patients at high risk of cerebrovascular diseases as ischemic changes in certain parts of the brain that control visuo-tactile perception, which may contribute to the development of secondary DI. It may be challenging to obtain the agreement of many of these patients for brain imaging studies because the nature of their delusion makes them averse to such a line of investigation, but is still worthy of consideration. Given the paucity of functional imaging studies, functional imaging studies are needed to elucidate the connectivity of important structures identified in this review. Future longitudinal research with a larger patient population, especially in patients with

primary DI, is recommended to continue investigating a possible link between DI and brain abnormalities.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

- Koo J, Lee CS. Delusions of parasitosis. A dermatologist's guide to diagnosis and treatment. *Am J Clin Dermatol.* 2001;2:285-90. [PMID: 11721647].
- Foster AA, Hylwa SA, Bury JE, et al. Delusional infestation: clinical presentation in 147 patients seen at Mayo Clinic. *J Am Acad Dermatol.* 2012;67:673.e1-10. [PMID: 22264448].
- Patru MC, Reser DH. A New Perspective on Delusional States - Evidence for Claustrum Involvement. *Front Psychiatry.* 2015;6:158. [PMID: 26617532].
- Vawter MP, Thatcher L, Usen N, et al. Reduction of synapsin in the hippocampus of patients with bipolar disorder and schizophrenia. *Mol Psychiatry.* 2002;7:571-8. [PMID: 12140780].
- Neves Mde C, Duarte DG, Albuquerque MR, et al. Neural correlates of hallucinations in bipolar disorder. *Braz J Psychiatry.* 2016;38:1-5. [PMID: 26785108].
- Radaelli D, Poletti S, Gorni I, et al. Neural correlates of delusion in bipolar depression. *Psychiatry Res.* 2014;221:1-5. [PMID: 24200366].
- Wolf RC, Huber M, Depping MS, et al. Abnormal gray and white matter volume in delusional infestation. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;46:19-24. [PMID: 23791615].
- Wolf R, Huber M, Lepping P, et al. Source-based morphometry reveals distinct patterns of aberrant brain volume in delusional infestation. *Prog Neuropsychopharmacol Biol Psychiatry.* 2014;48:112-6. [PMID: 24120443].
- Huber M, Wolf RC, Lepping P, et al. Regional gray matter volume and structural network strength in somatic vs. non-somatic delusional disorders. *Prog Neuropsychopharmacol Biol Psychiatry.* 2018;82:115-22. [PMID: 29180231].
- Krämer J, Huber M, Mundinger C, et al. Abnormal cerebellar volume in somatic vs. non-somatic delusional disorders. *Cerebellum Ataxias.* 2020;7:2. [PMID:31993210].
- Winkler AM, Kochunov P, Blangero J, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage.* 2010;53:1135-46. [PMID: 20006715].
- DeLong MR, Alexander GE, Georgopoulos AP, et al. Role of basal ganglia in limb movements. *Hum Neurobiol.* 1984;2:235-44. [PMID: 6715208].
- Freudenmann RW, Kolle M, Huwe A, et al. Delusional infestation: neural correlates and antipsychotic therapy investigated by multimodal neuroimaging. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010;34:1215-22. [PMID: 20600460].
- Huber M, Kirchlner E, Karner M, Pycha R. Delusional parasitosis and the dopamine transporter. A new insight of etiology? *Med Hypotheses.* 2007;68:1351-8. [PMID: 17134847].
- Ponson L, Andersson F, El-Hage W. Neural correlates of delusional infestation responding to aripiprazole monotherapy: a case report. *Neuropsychiatr Dis Treat.* 2015;11:257-61. [PMID: 25673993].
- Eccles JA, Garfinkel SN, Harrison NA, et al. Sensations of skin infestation linked to abnormal frontolimbic brain reactivity and differences in self-representation. *Neuropsychologia.* 2015;77:90-6. [PMID: 26260311].
- Burda JE, Sofroniew MV. Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron.* 2014;81:229-48. [PMID: 24462092].
- Hirjak D, Huber M, Kirchlner E, et al. Cortical features of distinct developmental trajectories in patients with delusional infestation. *Prog Neuropsychopharmacol Biol Psychiatry.* 2017;76:72-9. [PMID: 28257853].
- Maher BA. Delusional thinking and perceptual disorder. *J Individ Psychol.* 1974;30:98-113. [PMID: 4857199].
- Coltheart M. Cognitive neuropsychiatry and delusional belief. *Q J Exp Psychol (Hove).* 2007;60:1041-62. [PMID: 17654390].
- Coltheart M, Langdon R, McKay R. Delusional belief. *Annu Rev Psychiatry.* 2011;62:271-98. [PMID: 20731601].
- Hirjak D, Huber M, Kirchlner E, et al. Cortical features of distinct evolutionary trajectories in patients with delusional infestation. *Prog Neuropsychopharmacol Biol Psychiatry.* 2017;76:72-79. [PMID: 28257853].
- Palaniyappan L, Liddle PF. Dissociable morphometric differences of the inferior parietal lobule in schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* 2012;262:579-87. [PMID: 22454243].
- Dean K, Fearon P, Morgan K, et al. Grey matter correlates of minor physical anomalies in the AeSOP first-episode psychosis study. *Br J Psychiatry.* 2006;189:221-8. [PMID: 16946356].
- Huber M, Karner M, Kirchlner E, et al. Striatal lesions in delusional parasitosis revealed by magnetic resonance imaging. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32:1967-71. [PMID: 18930778].
- Groenewegen HJ. The basal ganglia and motor control. *Neural Plast.* 2003;10:107-20. [PMID: 14640312].
- Prevosto V, Graf W, Ugolini G. Proprioceptive pathways to posterior parietal areas MIP and LIPv from the dorsal column nuclei and the postcentral somatosensory cortex. *Eur J Neurosci.* 2011;33:444-60. [PMID: 21226771].
- Corlett PR, Taylor JR, Wang XJ, et al. Toward a neurobiology of delusions. *Prog Neurobiol.* 2010;92:345-69. [PMID: 20558235].
- Mochizuki H, Hernandez LE, Yosipovitch G, et al. The Functional Network Processing Acute Electrical Itch Stimuli in Humans. *Front Physiol.* 2019;10:555. [PMID: 31156452].
- Failla MD, Peters BR, Karbasforoushan H, et al. Intra-insular connectivity and somatosensory responsiveness in young children with ASD. *Mol Autism.* 2017;8:25. [PMID: 28630661].
- Flynn FG, Cummings JL, Scheibel J, Wirshing W. Monosymptomatic delusions of parasitosis associated with ischemic cerebrovascular disease. *J Geriatr Psychiatry Neurol.* 1989;2:134-9. [PMID: 2590374].
- Duggal H, Singh I. Delusional parasitosis as a presenting feature of dementia. *J Neuropsychiatry Clin Neurosci.* 2010; 22:123.e11-12. [PMID: 20160227].
- Burgy M. The concept of psychosis: historical and phenomenological aspects. *Schizophr Bull.* 2008;34:1200-10. [PMID: 18174608].
- Karlsgodt KH, Sun D, Cannon TD. Structural and Functional Brain Abnormalities in Schizophrenia. *Curr Dir Psychol Sci.* 2010;19:226-

31. [PMID: 25414548].
35. Loch AA. Schizophrenia, Not a Psychotic Disorder: Bleuler

Revisited. *Front Psychiatry*. 2019;10:328. [PMID: 31133901].

Table 1. Summary of structural MRI studies.

Study	Number of patients/number of controls	Method	Findings
Wolf et al. 2013 [7]	<u>16 DI patients</u> -6 Primary -3 Secondary to Psychiatric Depression -7 Secondary to Medical Condition <u>16 controls</u>	MRI (Voxel-based morphometry)	-Compared to controls, DI patients have lower gray matter volume in frontal regions, temporal regions, left subcallosus gyrus, left anterior cingulate gyrus, bilateral insula, right striatum, left thalamus -Compared to controls, DI patients have higher white matter volume in the right middle cingulate, gyrus, left frontal opercular, and bilateral striatal caudate, putamen -No abnormalities were found in parietal structures, but found structural pathologies in dopaminergic striatum (caudate, putamen)
Wolf et al. 2014 [8]	<u>16 DI patients</u> -6 Primary -3 Secondary to Psychiatric Depression -7 Secondary to Medical Condition <u>16 controls</u>	MRI (Source-based morphometry)	-Compared to controls, DI patients had lower gray matter volume in frontal, temporal, parietal, insular, thalamic, and striatal regions. Notable, Wolf et al. found no abnormalities in parietal structures. -Compared to controls, only patients with organic DI showed significantly increased WMV. No WMV changes were found in controls or primary/secondary to psychiatric depression patients -These results emphasize that the bilateral striatal and thalamic regions are affected compared to previous unilateral results
Hirjak et al. 2017 [18]	<u>18 DI patients</u> -6 primary -3 Secondary to Psychiatric -9 Organic <u>20 controls</u>	MRI (Surface-based morphometry)	-Cortical Thickness: Patients with DI had higher cortical thickness in the right medial orbitofrontal gyrus compared to controls. -Cortical Surface Area: Patients with DI had smaller cortical area in the left inferior temporal gyrus, the left precuneus, the pars orbitalis of the right frontal gyrus, and the right lingual gyrus -Cortical Gyrification: Patients with DI show reduced cortical gyrification in the left precentral gyrus, the left postcentral gyrus, the right precentral gyrus, the middle temporal gyrus, the banks of the right superior temporal sulcus, the right inferior parietal gyrus, and the right superior parietal gyrus
Huber et al. 2018 [9]	<u>18 DI patients</u> -6 primary -3 Secondary to Psychiatric -9 Organic <u>20 non-somatic delusions</u> <u>20 controls</u>	MRI (Voxel-based morphometry, Surface-based morphometry, Source-based morphometry)	-Patients with DI exhibit a pattern of lower GMV in fronto-thalamo-striatal and frontotemporal regions. -Striatal and frontotemporal network strength was lower in DI compared to patients with non-somatic delusions and HC -Compared to controls, patients with DI had lower GM in medial and lateral prefrontal areas, medial and lateral regions of the temporal lobe (including the hippocampus and parahippocampus), bilateral fusiform cortices, subcallosal and anterior cingulate cortices, bilateral insula, left putamen, left thalamus and left cerebellum -Compared to controls, patients with delusions other than DI showed lower GMV in the left inferior temporal cortex and the right fusiform cortex.
Krämer et al. 2020 [10]	<u>14 DI patients</u> -7 secondary or comorbid to medical conditions <u>18 non-somatic delusional patients</u> <u>18 patients with schizophrenia</u> <u>32 controls</u>	MRI (Voxel-based morphometry)	-Comparing DI patients to controls, there was lower GMV in left lobule VIIIa. -Comparing DI patients to non-somatic patients, they found lower GMV in lobule V and higher GMV in lobule V and higher GMV in bilateral lobule VIIa/crusII. -Comparing DI patients to schizophrenic patients, a lower GMV was found in lobule V, but that is was not statistically significant -Alternations in GMV found in schizophrenic patients differed from controls and DI patients.

GMV = Gray Matter Volume; WMV = White Matter Volume.

Table 2. Cases involving caudate nucleus.

Case	Age/ Sex	Classification	Past Medical History	Symptoms	Clinical Course	Imaging Modality	Laterality	Imaging Findings
1 [25]	74/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis	Feeling and seeing lice, insects, flies biting her hands, arms and head with severe pruritus	Imaging done 1 year after onset, full remission after haloperidol 1-3mg daily for 3 years	MRI	Right	Small lesion on the border with external capsule
2 [25]	83/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis, CHD, osteoporosis	Feeling insects biting her head and legs	Imaging done 10 years after onset, full remission after risperidone 1-2mg daily for 8 months	MRI	Left	Small lesion
3 [25]	81/M	Secondary to general medical condition	Hypertension, treated for >30 years, COPD, cholangiocarcinoma for 1 year	Feeling and seeing flies, insects, lice biting his body and mostly the head, hands, and arms	Imaging done 7 years after onset, full remission after olanzapine 10mg daily for 9 years	MRI	Left, Right	Macroscopic lesion
4 [25]	75/F	Secondary to general medical condition	Left temporal meningioma s/p resection 8 years ago, atrial fibrillation, hypertension, osteoporosis, hyperthyroidism s/p radiotherapy 3 years ago	Feeling and seeing vermin crawling on scalp with persistent pruritus on the head	Imaging done 40 years after onset, partial remission after risperidone 1-2mg daily for 1 month, followed by refusal of psychiatric treatment for 10 years, then partial remission after aripiprazole 10mg daily for 1 month	MRI	Left	Gliosis in outer margin
1 [36]	71/F	Secondary to general medical condition	Neurocysticercosis s/p treatment with albendazole and steroid, cognitive decline, hypertriglyceridemia, hypercholesterolemia	Feeling small animals living in her skin with sensation of pruritus	Imaging done 2 years after onset, no response after trials of sertraline 50mg daily, quetiapine 50mg daily, duloxetine 60mg daily, or risperidone 3mg daily	MRI	Left	Multiple well-delimited rounded lesions surrounded by edema
1 [13]	27/F	Secondary to substance use	Polysubstance abuse (methamphetamine up to 3g daily months and ecstasy up to 10 pills daily for 6 months, cannabis up to 8 joints daily for 4.5 years, alcohol binges)	Feeling small bugs on her skin and generalized pruritus	Imaging done 4.5 years after onset, full remission after risperidone 6mg daily with relapse after suspension of risperidone due to weight gain. Full remission after aripiprazole 10mg daily	PET, SPECT	Left, Right	Bilateral: reduced presynaptic dopamine turnover; focal D2-receptor availability

1 [37]	82/M	Secondary to general medical condition	Right temporal lobe infarction 5 years ago, cognitive decline	Feeling "tiny tick-like worms" crawling under his skin in the lower abdomen and limbs	Imaging done 5 years after onset, full remission after risperidone 1-2mg daily for 2 weeks	MRI, SPECT	Left, Right	Bilateral: decreased regional cerebral blood flow (rCBF)
10 [38]	86/F	Secondary to general medical condition	Deafness since age 67, hyperthyroidism s/p thyroidectomy at age 62, Fahr's disease, hyperuricemia since age 80, parkinsonism since age 80, CHF with cardiac pacemaker after age 81, 2 minor CVAs at age 79 and 86	Feeling and seeing vermin crawling on scalp, nose, and mouth with severe pruritus	Imaging done 14 years after onset, full remission after quetiapine 75-600mg daily for 2 years	CT	Right	Post-ischemic lacunar lesion in the head
13 [38]	85/F	Secondary to general medical condition	Cerebrovascular insufficiency, bipolar disorder treated for 39 years, multiple arthrosis	Feeling and seeing small white "critters" biting her hands, arms and head with severe pruritus	Imaging done 2 years after onset, full remission after ziprasidone 80mg daily for 5 months	MRI	Right	Small lesion in the head
16 [38]	77/F	Secondary to general medical condition	Cerebral ischemic insults, CHD s/p left heart bypass and aortic valve replacement at age 73, mild DM2, mild Parkinson's disease, mild anemia	Feeling small penetrative/stinging organisms attacking her arms, head and body with severe pruritus	Imaging done 1 year after onset, full remission after haloperidol 1-2mg daily for 4 years	CT	Right	Hypodense lesions

Table 3. Cases involving putamen.

Case	Age/ Sex	Classification	Past Medical History	Symptoms	Clinical Course	Imaging modality	Laterality	Imaging Findings
1 [25]	74/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis	Feeling and seeing lice, insects, flies biting her hands, arms and head with severe pruritus	Imaging done 1 year after onset, full remission after haloperidol 1-3mg daily for 3 years	MRI	Left	Small lacunar lesion in posterior aspect
2 [25]	83/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis, CHD, osteoporosis	Feeling insects biting her head and legs	Imaging done 10 years after onset, full remission after risperidone 1-2mg daily for 8 months	MRI	Left, Right	Left: small lesion in anterior portion; Right: two very small lesions in outer portion
3 [25]	81/ M	Secondary to general medical condition	Hypertension, treated for >30 years, COPD, cholangiocarcinoma for 1 year	Feeling and seeing flies, insects, lice biting his body and mostly the head, hands, and arms	Imaging done 7 years after onset, full remission after olanzapine 10mg daily for 9 years	MRI	Left	Macroscopic lesion in mid posterior portion
4 [25]	75/F	Secondary to general medical condition	Left temporal meningioma s/p resection 8 years ago, atrial fibrillation, hypertension, osteoporosis, hyperthyroidism s/p radiotherapy 3 years ago	Feeling and seeing vermin crawling on scalp with persistent pruritus on the head	Imaging done 40 years after onset, partial remission after risperidone 1-2mg daily for 1 month, followed by refusal of psychiatric treatment for 10 years, then partial remission after aripiprazole 10mg daily for 1 month	MRI	Left, Right	Left: gliosis in outer margin; Right: small lesion in mid portion
1 [13]	27/F	Secondary to substance use	Polysubstance abuse (methamphetamine up to 3g daily months and ecstasy up to 10 pills daily for 6 months, cannabis up to 8 joints daily for 4.5 years, alcohol binges)	Feeling small bugs on her skin and generalized pruritus	Imaging done 4.5 years after onset, full remission after risperidone 6mg daily with relapse after suspension of risperidone due to weight gain. Full remission after aripiprazole 10mg daily	PET, SPECT	Left, Right	Left: markedly reduced presynaptic dopamine transporter availability; increased glucose metabolism; Bilateral: focal D2-receptor availability
2 [13]	72/F	Secondary to general medical condition	Rheumatoid arthritis, hypertension	Feeling small pests, animals, and splinters infesting her hair, ears, nose, feet, axillae, and left shoulder	Imaging done 2 years after onset, no response to quetiapine 50mg daily, partial remission after	MRI	Left, Right	Bilateral: Increased brain perfusion, significantly increased

					ziprasidone 80mg daily			gray matter volume compared to age-matched controls
1 [37]	82/M	Secondary to general medical condition	Right temporal lobe infarction 5 years ago, cognitive decline	Feeling "tiny tick-like worms" crawling under his skin in the lower abdomen and limbs	Imaging done 5 years after onset, full remission after risperidone 1-2mg daily for 2 weeks	MRI, SPECT	Left, Right	Bilateral: decreased regional cerebral blood flow (rCBF)
10 [38]	86/F	Secondary to general medical condition	Deafness since age 67, hyperthyroidism s/p thyroidectomy at age 62, Fahr's disease, hyperuricemia since age 80, parkinsonism since age 80, CHF with cardiac pacemaker after age 81, 2 minor CVAs at age 79 and 86	Feeling and seeing vermin crawling on scalp, nose, and mouth with severe pruritus	Imaging done 14 years after onset, full remission after quetiapine 75-600mg daily for 2 years	CT	Right	Post-ischemic lacunar lesion
16 [38]	77/F	Secondary to general medical condition	Cerebral ischemic insults, CHD s/p left heart bypass and aortic valve replacement at age 73, mild DM2, mild Parkinson's disease, mild anemia	Feeling small penetrative/stinging organisms attacking her arms, head and body with severe pruritus	Imaging done 1 year after onset, full remission after haloperidol 1-2mg daily for 4 years	CT	Right	Hypodense lesions

Table 4. Cases involving *centrum semiovale*.

Case	Age/ Sex	Classification	Past Medical History	Symptoms	Clinical Course	Imaging modality	Laterality	Imaging Findings
1 [25]	74/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis	Feeling and seeing lice, insects, flies biting her hands, arms and head with severe pruritus	Imaging done 1 year after onset, full remission after haloperidol 1-3mg daily for 3 years	MRI	Bilateral	Macroscopic asymmetric lesions
2 [25]	83/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis, CHD, osteoporosis	Feeling insects biting her head and legs	Imaging done 10 years after onset, full remission after risperidone 1-2mg daily for 8 months	MRI	Bilateral	Several small lesions
3 [25]	81/M	Secondary to general medical condition	Hypertension, treated for >30 years, COPD, cholangiocarcinoma for 1 year	Feeling and seeing flies, insects, lice biting his body and mostly the head, hands, and arms	Imaging done 7 years after onset, full remission after olanzapine 10mg daily for 9 years	MRI	Bilateral	Macroscopic lesions
7 [38]	73/M	Secondary to pre-existing psychiatric illness	Depression for 25 years, mild hypertension, rectal carcinoma s/p resection 9 years ago, syringomyelia	Feeling and hearing vermin coming out of the nose and mouth and crawling on his scalp, eyes, and chest	Imaging done 2 years after onset, full remission after risperidone 2mg daily for 3 years	MRI	Bilateral	Multiple lesions
13 [38]	85/F	Secondary to general medical condition	Cerebrovascular insufficiency, bipolar disorder treated for 39 years, multiple arthrosis	Feeling and seeing small white "critters" biting her hands, arms and head with severe pruritus	Imaging done 2 years after onset, full remission after ziprasidone 80mg daily for 5 months	MRI	Bilateral	Gliotic lesions
14 [38]	78/M	Primary delusional parasitosis	Parkinson's disease treated for 1 year	Feeling worms and vermin on his head with extensive trichotillomania	Imaging done 6 years year after onset, full remission after risperidone 2mg daily for 7 months	MRI	Bilateral	Multiple lesions
15 [38]	76/M	Primary delusional parasitosis	Parkinson's disease treated for 15 years, presbycusis since age 66	Feeling and seeing bugs and ants crawling on the head, arms, and legs	Imaging done 5 years after onset, full remission after quetiapine 200-300mg daily for 4 years	MRI	Bilateral	Unspecific hyperintensities
1 [39]	65/M	Secondary to general medical condition	History of traumatic right facial laceration at age 5	Feeling bugs in his cheeks, nose, mouth and ears with tingling and stabbing pains	Imaging done 7 years after onset, pimozide discontinued due to prolonged QTI, risperidone	MRI	Bilateral	Several scattered foci of increased T2 and

			complicated by keloid formation s/p multiple surgical revisions, history of cocaine abuse		discontinued due to akathisia, no response to quetiapine, partial response to olanzapine and gabapentin. Clinical Course complicated by relapse in cocaine use			FLAIR signal
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Table 5. Cases involving external capsule.

Case	Age/ Sex	Classification	Past Medical History	Symptoms	Clinical Course	Imaging modality	Laterality	Imaging findings
1 [25]	74/F	Secondary to general medical condition	Hypertension, treated for >10 years, cerebral arteriosclerosis	Feeling and seeing lice, insects, flies biting her hands, arms and head with severe pruritus	Imaging done 1 year after onset, full remission after haloperidol 1-3mg daily for 3 years	MRI	Right	2 small lesions in right mid portion
4 [25]	75/F	Secondary to general medical condition	Left temporal meningioma s/p resection 8 years ago, atrial fibrillation, hypertension, osteoporosis, hyperthyroidism s/p radiotherapy 3 years ago	Feeling and seeing vermin crawling on scalp with persistent pruritus on the head	Imaging done 40 years after onset, partial remission after risperidone 1-2mg daily for 1 month, followed by refusal of psychiatric treatment for 10 years, then partial remission after aripiprazole 10mg daily for 1 month	MRI	Left	Gliososis
2 [36]	72/F	Secondary to general medical condition	Cerebrovascular disease, diabetic neuropathy, radiculopathy, hypertension, major depressive disorder, cognitive decline	Feeling small bugs inside her vagina, rectum, and legs with sensation of itching and biting	Imaging done 1 year after onset, full remission after risperidone 2mg daily and duloxetine 60mg daily for 1 year, with relapse after suspension of risperidone due to sedation and rigidity. Partial remission after quetiapine 100mg daily	MRI	Left	Small ischemic lesion
10 [38]	86/F	Secondary to general medical condition	Deafness since age 67, hyperthyroidism s/p thyroidectomy at age 62, Fahr's disease, hyperuricemia since age 80, parkinsonism since age 80, CHF with	Feeling and seeing vermin crawling on scalp, nose, and mouth with severe pruritus	Imaging done 14 years after onset, full remission after quetiapine 75-600mg daily for 2 years	CT	Right	Post-ischemic lacunar lesion

			cardiac pacemaker after age 81, 2 minor CVAs at age 79 and 86					
13 [38]	85/F	Secondary to general medical condition	Cerebrovascular insufficiency, bipolar disorder treated for 39 years, multiple arthrosis	Feeling and seeing small white "critters" biting her hands, arms and head with severe pruritus	Imaging done 2 years after onset, full remission after ziprasidone 80mg daily for 5 months	MRI	Bilateral	Gliotic lesions