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## Cotard syndrome in anti-NMDAR encephalitis: two patients and insights from molecular imaging

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### ABSTRACT

Cotard syndrome is a clinical condition defined by the presence of nihilistic delusions. We report two patients with Cotard syndrome in whom anti-NMDAR encephalitis (ANMDARE) was confirmed. Both cases showed features of affective psychosis, developed catatonic syndrome, and worsened after the use of antipsychotics. 18F-FDG PET brain studies showed a bilateral hemispheric pattern of hypometabolism in posterior regions, mainly in the cingulate cortex and in the medial aspects of parietal and occipital lobes. A more severe hypometabolism was observed in the right hemisphere of both patients. Both cases remitted with the use of specific immunotherapy for ANMDARE.

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### KEYWORDS

Cotard syndrome; nihilistic delusions; anti-NMDAR encephalitis; autoimmune encephalitis; molecular imaging

### Introduction

Cotard syndrome refers to a rare content-specific condition characterized by pathological beliefs of physical deterioration or death, also known as nihilistic delusions (Berrios & Luque, 1995a; Ramirez-Bermudez et al., 2010). Patients with Cotard syndrome may deny the existence of their body parts or their whole existence and claim to be dead (Berrios & Luque, 1995b). Some nihilistic delusions may be related to disturbances of extrapersonal space extending to objects in the world (Berrios & Luque, 1995b; Ramirez-Bermudez et al., 2010). These beliefs may be related to abnormal feelings of familiarity, as in delusional misidentification syndromes (Nishio & Mori, 2012).

Beginning with Jules Cotard's original descriptions in the 19th century, Cotard syndrome has been described in both neurological diseases and psychiatric disorders (Cotard & Berrios, 1999). There are reports of this syndrome in patients with viral encephalitis, autoimmune encephalitis, brain neoplasms, traumatic brain injury, cerebrovascular disease, and semantic dementia, as well as in psychotic depression and schizophrenia (Funayama et al., 2018; Mendez & Ramirez-Bermúdez, 2011; Restrepo-Martínez, Espinola-Nadurille, Bayliss, Díaz-Meneses, Kerik, Mendez, Ramírez-Bermúdez et al., 2019; Sahoo & Josephs, 2017). Recently, a case of Cotard syndrome in anti-NMDAR encephalitis (ANMDARE) was reported (Funayama et al., 2018).

Although there have been several attempts to understand Cotard syndrome pathophysiology, causal factors and psychobiological mechanisms of nihilistic delusions are still unclear. As it is unlikely that delusions are susceptible to simple localizationist theories, we pose that through the study of patients with neurological disorders such as ANMDARE, that compromise the function of several brain networks (Kerik-Rotenberg

et al., 2019), and with the help of molecular imaging, advanced hypothesis could be developed to explain the underlying brain processes in Cotard syndrome. Therefore, we have conducted a study to discriminate the presence of Cotard syndrome in a cohort of patients with ANMDARE. Through the findings of brain 18 F-FDG-PET of these patients, we aim to elucidate further functional neuroanatomical discussion in light of current psychopathological models of Cotard syndrome.

As part of a prospective and longitudinal study of patients with ANMDARE seen at the National Institute of Neurology and Neurosurgery of Mexico (Espinola-Nadurille et al., 2019) we registered the neuropsychiatric signs and symptoms of all patients with definite ANMDARE according to Graus criteria (Graus et al., 2016) over a six-year period. Psychotic symptoms were registered using a systematic procedure, including visual and auditory hallucinations, as well as delusions. This information was obtained using direct interviews with the relatives and caregivers of the patients and recorded during the daily observation while they were hospitalized. Delusions were classified according to their content, including persecutory, grandiose, jealousy, and nihilistic delusions. Patients with nihilistic delusions were classified as having stable and well established or transitory and unstable forms of nihilistic delusion. Patients with stable forms of delusional nihilism were assessed by means of a structured interview designed to assess the original features described by Jules Cotard (Cotard & Berrios, 1999), the statistical analysis of historical cases provided by Berrios et al., (Berrios & Luque, 1995b) and our previous psychopathological research in cases of Cotard syndrome (Mendez & Ramirez-Bermúdez, 2011; Ramirez-Bermudez et al., 2010; Restrepo-Martínez, Espinola-Nadurille, Bayliss, Díaz-Meneses, Kerik, Mendez, Reagan et al., 2019).

We established definite cases of ANMDARE through the detection of NMDAR-antibodies against the NR1 subunit in cerebrospinal fluid (CSF). These were obtained with rat brain immunohistochemistry and cell-based assays with NMDA expressing cells at Labco Nous Laboratories, Barcelona. Electroencephalogram (EEG) and brain magnetic resonance imaging (MRI), as well as brain and whole-body  $^{18}\text{F}$ -FDG-PET scans, were obtained. Nuclear medicine report was based on visual assessment of  $^{18}\text{F}$ -FDG-uptake distributions by two experts in metabolic imaging, and semiquantitative analysis with Syngo Scenium software (Siemens, Medical Solutions, Germany). Written informed consent was obtained from the patients before submitting this report.

From a total sample of 85 patients with ANMDARE, we found nine patients (10.6%) with nihilistic delusions. Seven cases expressed transitory and unstable forms of nihilist delusions within a pattern of multiple, not systematized, delusions with different topics. However, the other two patients had stable, well structured, persistent, and predominant nihilistic delusions, as follows:

### Case 1. Generalized nihilism in the context of collective disaster

Two days after the 2017 devastating Mexico City earthquake, a 37-year-old man, aid volunteer, and chiropractor started to feel progressively “weaker physically and mentally.” He experienced fear and guilt because “he couldn’t provide help when people most needed it.” He would speak in whispers, saying that his voice “had become low.” Over the next days, he exhibited headaches, insomnia, decreased appetite, irritability, auditory and visual hallucinations, delusions, and prolonged periods of mutism, and aggressive behavior toward himself and others. He also became paranoid, believing that his family wanted to harm him. The delusions of physical deterioration worsened. Risperidone (2 mg/day) and clonazepam (1 mg/day) were started as part of ambulatory psychiatric care. Three weeks after symptoms onset, he was admitted to the National Institute of Neurology and Neurosurgery (NINN) for self-injurious behavior. The patient had no personal or familial history of psychiatric illness.

On admission, he had fluctuating levels of consciousness with periods of psychomotor agitation, inattention, and disorientation. His neurological examination was otherwise normal. Brain MRI was unremarkable, but an EEG revealed a severe generalized slowing without epileptic activity. CSF analysis showed a moderate pleocytosis [(54 white blood cells/mm<sup>3</sup> (99% lymphocytes)], with proteins and glucose within normal ranges. Infectious etiologies were excluded, and NMDAR antibodies were requested.

The patient developed autonomic instability and catatonic features, including motor excitement alternating with immobility, mutism, staring, and posturing. Catatonia was treated with lorazepam (6 mg/day) and psychomotor agitation with quetiapine (300 mg/day). Over the following days, the patient developed increasing catatonic excitement with prominent stereotypes and verbigeration. The Bush and Francis Catatonia Rating Scale (BFCRS) increased from an initial score of 7/25 to a score of 11/34. The BFCRS measures the severity of

23 catatonic signs on a 0–3 scale, and is represented here as the “denominator”, while the BFCSI (Bush and Francis Catatonia Screening Index) evaluates only the presence and absence of the first 14 items, and is presented here as the “numerator” (Bush et al., 1996). Montreal Cognitive Assessment (MOCA) could not be obtained.

Anti-NMDAR antibodies appeared positive in CSF. A brain  $^{18}\text{F}$ -Fluoro-deoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) study revealed prominent hypometabolism in the occipito-parietal cortex bilaterally. This was more accentuated in the right hemisphere, comprising the dorsolateral and medial aspects of both lobes (Figure 1), notably including the pre-cuneus and the posterior cingulate cortex. The whole body  $^{18}\text{F}$ -FDG PET was negative for malignancies. The patient was then treated with methylprednisolone pulses and five sessions of plasma exchange.

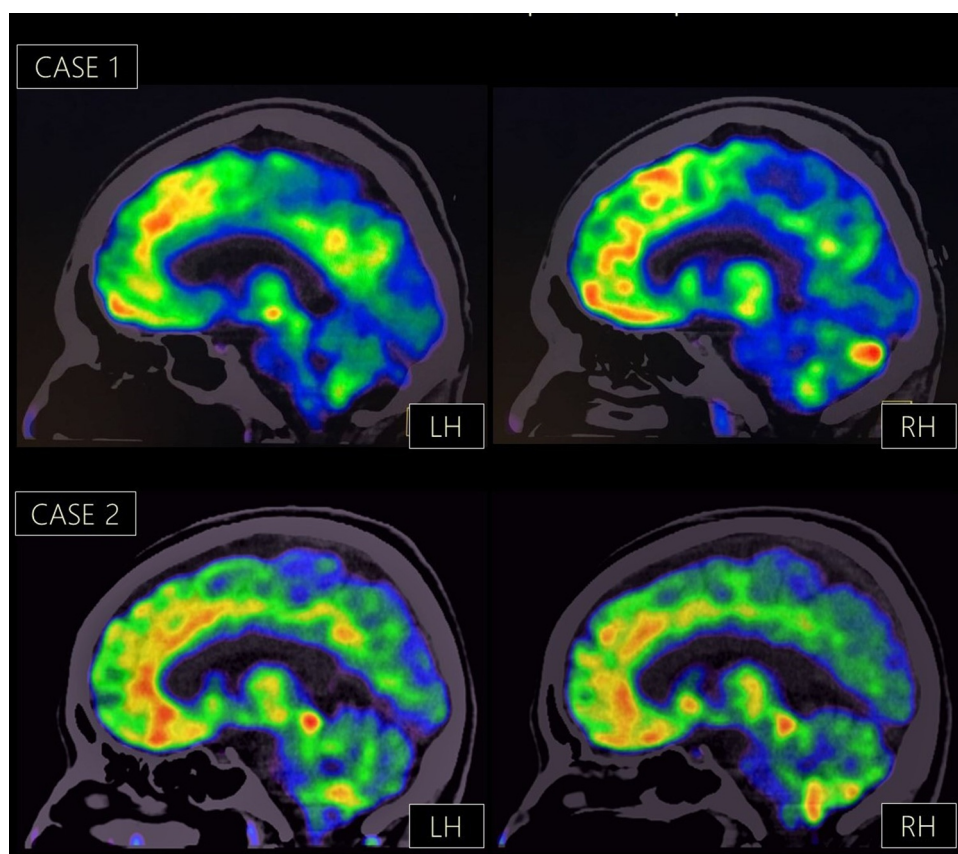
Four days after he received his fifth session of plasma exchange, his alertness improved, but psychotic symptoms remained. When asked how he felt, he answered: “I do not have feelings because I am dead ... All human beings will be dead.” He added that he had a “right-sided” heart and that it had stopped.

The patient was transferred to the neuropsychiatric unit. Over the following days, catatonic symptoms continued to improve (BFCRS score of 8/21), but nihilistic delusions persisted unchanged: “I am dead, among other human beings. This is like a program where I am dead”. The patient claimed to be a dead person among the corpses under the earthquake debris. Doctors and nurses were part of a game whose objective was to cover up his death. Table 1 shows the psychopathologic features of the Cotard syndrome of this case. At this point, olanzapine (20mg/day) was started in combination with lorazepam (8 mg/day), plus a dose of cyclophosphamide. Psychotic and catatonic symptoms slowly improved. He was discharged after 42 days of hospitalization, with remission of his symptoms. After a 5-month follow-up as an outpatient, he remained asymptomatic and had returned to work as a chiropractor.

### Case 2. Delirious mania progressing to catatonic nihilism

A 44-year-old woman developed a manic-like state of euphoria, hyperactivity, disinhibition, pressured speech, hypergraphia, decreased need for sleep, grandiose delusions, and aggressive behavior. A few days after, she started to ask whether her family had attended her funeral. Since she thought she had died, she told her husband to marry another woman and wrote a letter to her family, communicating the firm belief of being dead. Disorientation and fluctuating catatonic symptoms appeared, including excitation alternating with withdrawal, mutism, and refusal to eat and drink. She was admitted to a psychiatric hospital where olanzapine was started. A worsening in catatonic symptoms was observed. After a generalized tonic-clonic seizure, she was referred to the NINN. The patient had no family history of mood disorders, although she had a personal history of mild depressive symptoms at age 20, which resolved with use of psychotherapy without pharmacological treatment.

On admission, she was catatonic with fluctuating periods of stupor and psychomotor agitation. The Bush and Francis



**Figure 1.** 18F-FDG PET brain study in patients with cotard syndrome and anti-nmda receptor encephalitis. 18F-FDG PET brain studies in two patients with Cotard Syndrome and ANMDARE showed a bilateral hemispheric pattern of hypometabolism in posterior regions, mainly in the cingulate cortex and in the medial aspects of parietal and occipital lobes. A more severe hypometabolism was observed in the right hemisphere

**Table 1.** Psychopathologic features of cotard syndrome in two patients with and anti-nmdar encephalitis.

Clinical feature	CASE 1	CASE 2
<b>Core features (nihilistic delusions)</b>		
Nihilistic delusions related to body parts	Present	Absent
Nihilistic delusions related to the patient own existence	Present	Absent
Nihilistic delusions related to the patient own life	Present	Present
Nihilistic delusions related to the world or other persons	Present	Absent
<b>Additional features related to Cotard syndrome</b> (Berrios & Luque, 1995b)		
Delusions of immortality	Absent	Absent
Insensitivity to pain	Present	Present
Delusions of damnation	Absent	Absent
Depression	Present	Absent
Anxiety	Present	Absent
<b>Additional features related to Cotard syndrome</b> (Berrios & Luque, 1995b)		
Auditory hallucinations	Present	Absent
Visual hallucinations	Present	Absent
Delusions of guilt	Present	Absent
Hypochondriacal delusion	Present	Absent
<b>Additional features related to Cotard syndrome</b> (Mendez & Ramírez-Bermúdez, 2011; Ramírez-Bermudez et al., 2010; Restrepo-Martínez et al., 2019)		
Depersonalization/derealization	Absent	Absent
Psychomotor inhibition	Present	Present
Alexithymia	Present	Present
Negativism	Present	Present
Withdrawal	Present	Present
Suicidal ideation/behavior	Present	Absent

Catatonía Rating Scale (BFCRS) score was 8/25. Leukocytosis and creatinine phosphokinase (CPK) values of 582 were

observed. Lorazepam (6 mg/d) and quetiapine (300 mg/d) were started; however, after 1 day fever and rigidity were observed, stupor, autonomic instability, and leukocytosis worsened, and CPK levels increased to 3087. Lorazepam was maintained, and after quetiapine was discontinued, CPK values and autonomic instability improved gradually. Brain MRI and CSF analysis were unremarkable. EEG revealed a severe dysfunction with dominant delta waves. A brain  $^{18}\text{F}$ -FDG PET, performed two days after admission, showed a marked occipital hypometabolism, as well as a bilateral hypometabolism in the medial aspects of the parietal lobe, including the precuneus (Figure 1). The determination of CSF anti-NMDAR antibodies was positive, and first-line immunotherapy was started.

After treatment with methylprednisolone and immunoglobulin, the patient showed a slow recovery from delirium and catatonia. As cognitive function improved, she resumed daily activities like taking a bath by herself, walking, and reading. However, memory, language, and orientation disturbances persisted. A new EEG showed a mild to moderate generalized dysfunction, with dominant theta waves. After 25 days of inpatient treatment, she had a Montreal Cognitive Assessment (MOCA) score of 13/30.

In this context, she refused to eat due to delusional thinking. Once again, she told her husband she was dead, asked him if her family had been to her funeral, and instructed him to remarry for she was already dead. Table 1 shows the psychopathologic features of the Cotard syndrome in this case. She



was treated with amisulpride (400 mg/day), achieving a full remission of nihilistic delusions. Antipsychotic medication was suspended after a month, and at a four-month follow-up, she showed complete recovery from any psychotic symptoms, although cognitive function remained affected (MOCA score of 21/30). After recovery, the patient explained that during the acute phase of catatonia, she thought that she was dead because of the feeling that time was passing extremely slow, and because she could not talk or move despite her will.

## Discussion

Like many other psychiatric diagnoses from the neuropsychiatric tradition, Cotard syndrome has been left out of the DSM-5 and the International Classification of Disease (American Psychiatric Association, 2013; World Health Organization, 1993). The lack of diagnostic criteria or clinimetric instruments is an important limitation toward increased recognition and research of this entity. According to the features documented since Jules Cotard's first observations, we have conducted a structured interview to register core and related symptoms of Cotard syndrome for both patients (Berrios & Luque, 1995b, 1995a; Restrepo-Martínez, Espinola-Nadurille, Bayliss, Díaz-Meneses, Kerik, Mendez, Ramírez-Bermúdez et al., 2019). This attempt of systematization may be useful in the design of a clinical scale for diagnosis or severity rating, and a necessary step toward a scientific understanding of nihilistic delusions.

To our knowledge, only one previous case of Cotard syndrome in ANMDARE has been documented: the case of a 31-year-old nurse who experienced depersonalization, suicidal attempts, status epilepticus, and nihilistic delusions related to her heart, blood, and about not being alive (Funayama et al., 2018). Nonetheless, our current study suggests that nihilistic delusions may be not infrequent in the context of ANMDARE. About 10% of the cases from our cohort showed this kind of delusions during their clinical course, and two patients developed a full-blown Cotard syndrome in the context of catatonia. Interestingly, both patients with Cotard syndrome showed an improvement of catatonia, delirium, and psychomotor agitation after immunotherapy, but symptoms related to Cotard syndrome persisted for several days. Small doses of atypical antipsychotics were required to achieve complete symptomatic remission. Table 2 summarizes previous reports of Cotard syndrome in the context of autoimmune (or infectious) encephalitis.

In our patients, Cotard syndrome occurred before, during, and after they were in a catatonic stage of ANMDARE, suggesting a relationship between both phenomena. Patients with NMDAR-antibodies encephalitis may exhibit a wide range of catatonic signs, which are observed in 32–70% of these patients (Espinola-Nadurille et al., 2019; Warren et al., 2018). Catatonia occurs as part of a sequence of symptoms in the clinical course of ANMDARE. Neurobehavioral changes proceed through stages that include prodromal, psychotic, catatonic, and hyperkinetic stages, as in our patients (Venkatesan & Adatia, 2017).

A cohort of 100 patients showed that 77% started with psychiatric symptoms, and most of these patients were evaluated initially by psychiatrists (Dalmau et al., 2008). A broad spectrum of psychiatric abnormalities has been reported in

**Table 2.** Cotard syndrome in patients with autoimmune or viral encephalitis.

Study	Patient	Brain imaging findings
(McKay & Cipolotti, 2007)	1 case with Herpes virus encephalitis	MRI: abnormal T2 high signal in the insula, claustrum and adjacent white matter on the right hemisphere. Less severe changes in the left insular cortex
(Ramirez-Bermudez et al., 2010)	1 case with acute encephalitis	MRI: No significant abnormalities
(Funayama et al., 2018)	1 case with anti-NMDAR encephalitis	MRI: No significant abnormalities
(Hajnal & Lazary, 2019)	1 case with Hashimoto encephalopathy	MRI: Disseminated white matter lesions on both cerebral hemispheres, mainly in the right frontal lobe
(Restrepo-Martínez et al., 2019)	1 case with autoimmune encephalitis (NMDAR antibodies-negative)	MRI: No significant abnormalities FDG-PET: Abnormalities in prefrontal cortex, insular cortex and occipital lobe, before treatment, with recovery of prefrontal cortex and occipital lobe metabolism after treatment.

ANMDARE. Psychomotor agitation and aggressive behavior are the most frequent of these features but psychotic symptoms are also frequent, occurring in 45–67% of the patients (Al-Diwani et al., 2019; Warren et al., 2018), especially in association with signs of encephalopathy or delirium (Espinola-Nadurille et al., 2018). Both of our patients were in states of delirium on admission, consistent with the EEG results, which showed severe generalized slowing. Patients with ANMDARE are often classified as having psychosis from the affective or schizophrenia spectrums. In order to treat agitation, patients may receive high potency antipsychotics to which they have shown an increased intolerance and risk of neuroleptic malignant syndrome according to some (not all) studies (Lejoste et al., 2016; Warren et al., 2018; Nicola Warren et al., 2019). Warren et al, argue that potential side effects of antipsychotic treatment are difficult to differentiate from progression of ANMDARE (Nicola Warren et al., 2019). However, both of our cases had a clinical worsening after the use of antipsychotics, and case 2 developed neuroleptic malignant syndrome. Failure to recognize psychiatric presentations of ANMDARE may lead to significant delays in initiating immunotherapy. Recent conceptualizations of autoimmune psychosis could be helpful to recognize these psychiatric phenotypes (Pollak et al., 2019).

According to Davies et al., a two-factor hypothesis might explain the formation of monothematic delusions. The first factor typically refers to an abnormal perception leading to an exceptional subjective experience, while the second factor refers to an abnormality in the metacognitive ability to make judgments about one's beliefs and mental states. Under this model, the content of delusions is shaped by abnormal experiences arising from specific neuropsychological defects (Davies et al., 2001). For example, in Capgras syndrome, a defect in the affective response to faces has been proposed as an underlying perceptual dysfunction, merging from damaged connections from face-processing areas in the temporal lobe to the limbic system (Hirstein & Ramachandran, 1997). This would be the first

factor, whereas a lack of metacognitive reasoning would be the second factor. In contrast, Cotard patients show a more general flattening of affective responses to stimuli in which the defect may extend to any stimuli coming from exteroceptive, proprioceptive, and interoceptive sources (McKay & Cipolotti, 2007). Flattening to affective responses may result in a loss of intense emotional experiences and a feeling of emptiness that, in the context of an internalizing attributional style, would lead to delusions of somatic dysfunction, death, or nonexistence (Davies et al., 2001; McKay & Cipolotti, 2007).

Recent studies have suggested that patients with Cotard syndrome show structural or functional abnormalities in the paralimbic cortices involved in emotional consciousness, such as the insular cortex, that could represent the neural basis of a first factor necessary for the development of nihilistic delusions (Chatterjee & Mitra, 2015; Restrepo-Martínez, Espinola-Nadurille, Bayliss, Díaz-Meneses, Kerik, Mendez, Ramírez-Bermúdez et al., 2019). On brain  $^{18}\text{F}$ -FDG-PET, both of our patients showed bilateral hypometabolism in the occipital lobe and the parietal precuneus, with a more severe hypometabolism on the right side. Prior cases with Cotard syndrome have reported abnormalities in the posterior regions and occipital lobe with greater right hemisphere involvement (Sahoo & Josephs, 2017). A previous PET study also showed a hypometabolic pattern in regions related to the default mode network and self-integration: the precuneus, the posterior cingulate cortex, and mesial-frontal cortices (Charland-Verville et al., 2013). If a two-factor account for the development of delusions is considered, the involvement of the cortices mentioned above could alter normal feelings of familiarity toward oneself and the environment, possibly contributing to the mechanism behind nihilistic delusions. Bilateral parieto-occipital hypometabolism with involvement of the precuneus and posterior cingulate cortex has been reported as a characteristic feature of ANMDARE (Kerik-Rotenberg et al., 2019). The cases reported here had a more severe hypometabolism on the right hemisphere, something that is not observed in most cases of ANMDARE.

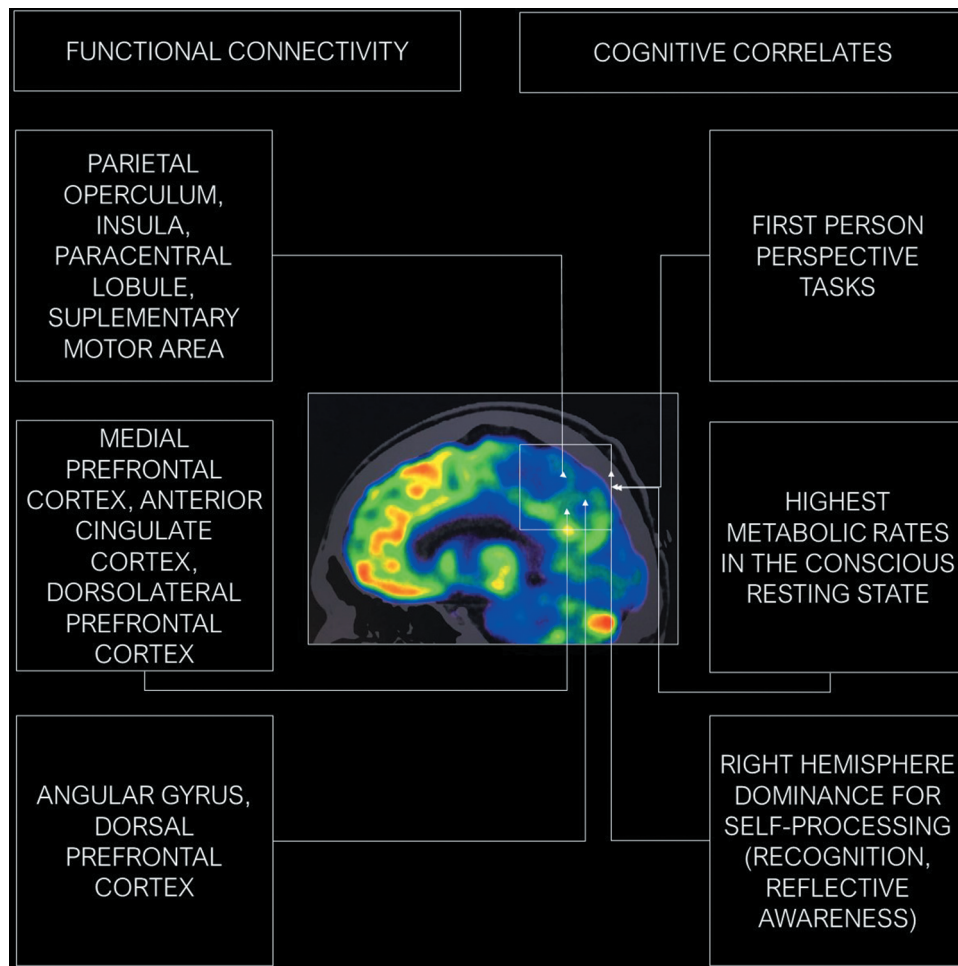
Following the two-factor account of monothematic delusions, the adoption and maintenance of delusions depend on a second factor: a failure in the cognitive systems for belief evaluation (Davies et al., 2001), possibly from frontal lobe dysfunction and decreased insight. We hypothesized that the marked cognitive dysfunction observed in our patients acted like a second factor leading to abnormal reasoning and a deficit in metacognitive abilities. This could be related in our case to encephalopathy, with a general decline in cognitive function, but also to the severe hypometabolism in medial parietal cortices, which are involved in mnemonic metacognition and to the integration of information from multiple sources, including autobiographical memory, interoceptive and exteroceptive sources (Davey & Harrison, 2018; Davey et al., 2016; Ye et al., 2018). The improvement in cognitive dysfunction was related in both cases to remission of delusional beliefs.

The connectivity and cognitive correlates of the medial parietal cortex (Brodmann areas 7, 23, 31) could be of interest in the search for a scientific hypothesis of Cotard syndrome. These are summarized in Figure 2, as this area showed a marked hypometabolism in our patients. Functional

connectivity studies in humans and monkeys (Margulies et al., 2009) show a relevant division: (1) The anterior part of the precuneus is connected with the parietal operculum, the paracentral lobule, the supplementary motor area, and the insula, suggesting a sensorimotor specialization. (2) The central precuneus is functionally connected to the dorsolateral and dorsomedial prefrontal cortex. The multimodal associative specialization of this region is also suggested by the connections with the lateral inferior parietal cortex. (3) The posterior cingulate cortex is functionally related to limbic regions: the medial temporal cortex, the anterior cingulate cortex, the ventromedial prefrontal region, but also the dorsolateral prefrontal cortex. These connectivity patterns suggest that the precuneus and the posterior cingulate cortex are involved in multimodal integration and bodily awareness (Herbet et al., 2019), emotional processing (Vogt, 2005), and metacognition (Ye et al., 2018). The disruption of this integrative activity could be a source of abnormal affective experience related to the perceptual-emotional disconnection seen in Cotard patients, and it may also generate a disturbance in the awareness necessary for metacognitive reasoning.

The posteromedial parietal cortex (including the precuneus, retrosplenial, and the posterior cingulate cortex) is one of the three major subdivisions that are part of the default mode network (DMN), together with the ventral medial prefrontal cortex and the dorsomedial prefrontal cortex (Cavanna, 2007; Raichle, 2015). The posterior elements of the DMN are known not only for their role in the recollection of prior experiences, but also for the integration of spatial and interoceptive representation of the body, and their activity during first-person perspective tasks (Cavanna & Trimble, 2006; Davey & Harrison, 2018; Raichle, 2015). Both anterior and posterior elements of the DMN act at the intersection of large scale networks, integrating information from multiple sources, including autobiographical memory and interoceptive processes, suggesting an active role of the DMN in the neural construction of the self (Davey & Harrison, 2018; Davey et al., 2016). Mnemonic metacognition (Ye et al., 2018) as well as emotional processing have also been related to neural activity at the level of precuneus and posterior cingulate cortex (Ye et al., 2018).

The study of neuropsychiatric patients with bodily awareness delusions, as somatoparaphrenia, has pointed out the role of precuneus in bodily awareness (Herbet et al., 2019). Clinical evidence points shows that the right hemisphere might have a predominant role in the formation of bodily awareness delusions (Baier & Karnath, 2008). During self-referential processing, the posterior cortices of the DMN coordinate the generation of self-representations, while the medial prefrontal cortex is involved in selecting and gating the representations into conscious awareness (Davey et al., 2016). Additionally, the DMN has also been proposed to be relevant in the understanding of self and others, using embodied simulation and mentalizing through close interaction with the mirror neuron system (MNS) (Molnar-Szakacs & Uddin, 2013). According to their FDG-PET, both patients presented in this study showed an impairment of the DMN, given mostly by the hypometabolism observed in its posterior hub (posteromedial parietal cortex). Thus, some of the nuclear symptoms of Cotard syndrome, including the different forms of self-denial and the failure of



**Figure 2.** Functional connectivity and cognitive correlates of the precuneus and posterior cingulate cortex. Patients with Cotard syndrome and anti-NMDAR encephalitis showed a marked hypometabolism in the medial aspects of parietal cortex, including the precuneus, and in the posterior cingulate cortex (Brodmann areas 7, 23, 31). This pattern was more severe in the right hemisphere. Main connectivity of these regions is shown (Margulies et al., 2009), as well as functional correlates (Cavanna, 2007; Cavanna & Trimble, 2006)

Cotard patients to assess themselves and others' physical and mental states, may arise in the context of a dysfunction of the posterior cortices of the DMN.

It is important to consider the lateralized hypometabolism found in the  $^{18}\text{F}$ -FDG PET of both patients. As many other delusional syndromes, nihilistic delusions seen in Cotard syndrome have shown a particular association with right hemisphere lesions, supported by structural and functional neuroimaging (Gurin et al., 2017; Nishio & Mori, 2012). Alterations in pragmatic communication, perceptual integration, attentional surveillance, and belief updating are some of the underlying mechanisms behind delusions development after right hemisphere dysfunction (Gurin et al., 2017). Furthermore, functional MRI has shown that fronto-parieto-occipital networks in the right hemisphere are critical for visual and auditory self-recognition (Kaplan et al., 2008).

Besides the inherent limitations of case studies, the PET images presented in this article were requested during the acute phase of the disease as these were necessary for the clinical assistance, and we cannot provide further information about possible neurotoxicity mediated by anti-NMDAR

antibodies. Furthermore, FDG-PET scans were performed during catatonic stages and the relationship of the abnormal metabolic pattern with Cotard syndrome requires further research, as both catatonia and ANMDARE itself are associated with distinct brain metabolic changes.

In summary, our study illustrates Cotard syndrome in ANMDARE, and demonstrates the course and management of these symptoms. During the presence of nihilistic delusions,  $^{18}\text{F}$ -FDG PET brain studies showed a bilateral hemispheric pattern of hypometabolism in posterior regions, mainly in the cingulate cortex and in the medial aspects of parietal and occipital lobes. A more severe hypometabolism was observed in the right hemisphere. This metabolic pattern supports the hypothesis of dysfunction in paralimbic and association cortices, which could lead to the altered perceptual-emotional integration and abnormal feelings of familiarity seen in patients with Cotard syndrome. Psychiatrists and other mental health professionals who see patients with new-onset nihilistic delusions, especially in the context of catatonic signs, need to consider ANMDARE as a potential diagnosis. This would allow prompt immunotherapy and guarantee caution when

antipsychotics are needed.

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