International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Where Neurology Meets Psychiatry: Exploring Rare Neuropsychiatric Syndromes and their Diagnostic Challenges: A Review of Anti-NMDA Receptor Encephalitis, Capgras Syndrome, Cotard's Syndrome, and Charles Bonnet Syndrome

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Abstract: ***Neurology and psychiatry, though historically treated as separate disciplines, converge sharply in a group of rare syndromes whose symptoms sit uneasily between the two fields. This paper examines four such conditions - anti-NMDA receptor encephalitis, Capgras syndrome, Cotard's syndrome, and Charles Bonnet syndrome- as a spectrum illustrating how disrupted neural circuitry can produce presentations that are readily mistaken for primary psychiatric illness. Drawing on published case reports, this review traces each syndrome's clinical presentation, proposed neurobiological mechanism, and pattern of misdiagnosis, then draws comparisons across the four to identify shared diagnostic pitfalls. The paper argues that these syndromes are not isolated curiosities but points along a continuum- from clear autoimmune pathology, to delusions with plausible neuroanatomical explanations, to hallucinations with fully preserved insight- and that recognizing this continuum has direct implications for clinical practice, particularly the need for closer collaboration between neurology and psychiatry in diagnostic workups.***

Keywords: Neuropsychiatry; Anti-NMDA receptor encephalitis; Capgras syndrome; Cotard's syndrome; Charles Bonnet syndrome; Autoimmune encephalitis; Delusional misidentification; Visual hallucinations; Differential diagnosis

1. Introduction

A 24-year-old woman was brought to the emergency department by her family after two weeks of increasingly bizarre behavior. She had become paranoid, accused coworkers of conspiring against her, and begun speaking in disorganized, tangential sentences. She was admitted to a psychiatric unit with a presumptive diagnosis of new-onset schizophrenia and started on antipsychotics. Over the following days, however, her condition diverged from the expected psychiatric course. She developed a low-grade fever, then repetitive orofacial movements, and finally a seizure. A neurology consult was called. Lumbar puncture and serum antibody testing confirmed anti-NMDA receptor encephalitis. She was transferred to neurology, treated with immunotherapy, and- after a prolonged recovery- returned largely to baseline.

Cases like this one, increasingly reported since the syndrome's characterization in 2007, illustrate a recurring diagnostic trap: a disorder with an identifiable autoimmune mechanism can present almost indistinguishably from a primary psychotic illness. A real, published example follows the same arc. In 2016, physicians in Japan described a 19-year-old woman with no prior psychiatric history who arrived at a district hospital with acute psychosis, emotional instability, and memory problems, and was admitted with a provisional diagnosis of dissociative disorder.[1] Her condition worsened- she developed aspiration pneumonia and required mechanical ventilation- before cerebrospinal fluid analysis and antibody testing confirmed anti-NMDA receptor encephalitis, a disorder first described in young women with ovarian teratomas whose antibodies attack a receptor densely expressed in the hippocampus.[1]

This paper examines four rare syndromes that expose the divide between neurology and psychiatry at its weakest points: anti-NMDA receptor encephalitis, Capgras syndrome, Cotard's syndrome, and Charles Bonnet syndrome. Each produces symptoms that, on the surface, look psychiatric- psychosis, delusions of impostors, delusions of death, vivid hallucinations- yet each has an identifiable, or at least plausible, neurological mechanism. Taken individually, these syndromes are often treated in the literature as isolated curiosities. Taken together, they form a spectrum. At one end sits anti-NMDAR encephalitis, an autoimmune disease with a clear, testable mechanism that happens to produce psychiatric symptoms first. At the other end sits Charles Bonnet syndrome, in which damaged visual pathways alone generate vivid hallucinations without any accompanying delusion or loss of insight. Between them sit Capgras and Cotard's syndromes, delusions that, while historically classified as psychiatric, are increasingly explained through specific disconnections between recognition and emotional processing in the brain.

This paper reviews each syndrome in turn, compares their mechanisms and diagnostic challenges, and argues that their combined lesson is a practical one: clinicians who treat "psychiatric" and "neurological" as mutually exclusive categories risk missing diagnoses that carry very different treatments and prognoses.

2. Background: The Neurology–Psychiatry Divide

The separation between neurology and psychiatry has roots stretching back to nineteenth-century medicine, when neurologists claimed authority over conditions with demonstrable lesions- strokes, tumors, epilepsy- while

psychiatrists took charge of conditions without one, often housed in separate institutions altogether: general hospitals for the former, asylums for the latter. This split hardened over the twentieth century, reinforced by different training pathways, different diagnostic manuals, and, for a period, competing theoretical frameworks- psychoanalysis on one side, biological reductionism on the other.

That divide has been steadily eroding for decades, but rarely because psychiatric conditions turned out to have no biological basis- rather because neurological ones turned out to have prominent psychiatric presentations, and vice versa. Conditions like epilepsy, multiple sclerosis, and Huntington's disease routinely produce mood disorders, psychosis, or personality change as core features rather than incidental complications. Conversely, autoimmune and paraneoplastic syndromes have revealed that a substantial minority of patients diagnosed with "primary" psychotic disorders are in fact experiencing an organic disease process with a specific, treatable cause.

The modern field of neuropsychiatry has emerged partly in response to this blurring, built on the recognition that many symptoms once assigned exclusively to one discipline or the other arise from shared neural circuitry- particularly limbic structures, frontotemporal networks, and their connections to sensory and associative cortex. The four syndromes reviewed in this paper sit squarely within that shared territory, and each offers a different demonstration of how a specific disruption to that circuitry can manifest as a symptom cluster that looks, on first presentation, purely psychiatric.

3. Case-by-Case Review

a) Anti-NMDA Receptor Encephalitis

Definition and Clinical Presentation
Anti-NMDA receptor (anti-NMDAR) encephalitis is an autoimmune disorder in which the body produces antibodies against NMDA receptors in the central nervous system- receptors essential to synaptic signaling, learning, and memory. The disease typically unfolds in stages. An early prodrome resembling a viral illness (headache, low-grade fever, malaise) is often followed within days to weeks by a florid psychiatric phase: agitation, paranoia, hallucinations, disorganized speech, and behavioral change severe enough to mimic a first-episode psychotic disorder. As the disease progresses, more clearly "neurological" features emerge- seizures, decreased consciousness, abnormal movements (particularly orofacial dyskinesias), and autonomic instability. It is this staged progression- psychiatric symptoms first, neurological signs later- that makes early cases so easy to misclassify.

Epidemiology
The disease was first characterized in 2007, initially in young women with ovarian teratomas, whose tumors were found to trigger the autoimmune response. Subsequent research has shown a broader picture: the condition affects both sexes and a wide age range, though it remains most common in young women, and a smaller proportion of cases are associated with an underlying tumor. It is considered rare but is now recognized as one of the more common causes of autoimmune encephalitis.

Proposed Neurobiological Mechanism
Antibodies target the NR1 subunit of the NMDA receptor, causing receptor internalization and a reduction in NMDA receptor density and function at synapses, particularly in the hippocampus and forebrain- regions central to memory, emotional regulation, and reality-testing. Because NMDA receptor hypofunction is also a longstanding pharmacological model for psychosis, the mechanism offers a direct, testable link between a specific molecular lesion and psychiatric symptomatology.

Diagnostic Criteria and Workup
Diagnosis relies on a combination of clinical suspicion, cerebrospinal fluid analysis, and antibody testing.[1] EEG often shows nonspecific slowing rather than clear epileptiform activity, and brain MRI is frequently normal or shows only subtle changes early in the disease course, which is part of why the diagnosis is so easily missed. Tumor screening is a standard part of the workup given the paraneoplastic association.

Common Misdiagnoses and Why They Happen
Because the earliest and most prominent symptoms are behavioral and psychiatric, and because initial imaging and routine labs are often unremarkable, patients are frequently first diagnosed with schizophrenia, dissociative disorder, bipolar disorder with psychotic features, or generalized anxiety disorder.[1] The diagnosis is typically only reconsidered once the illness progresses to more unambiguous neurological territory.

Treatment and Prognosis
Anti-NMDAR encephalitis has a clearly defined, mechanism-based treatment: immunotherapy (corticosteroids, IVIG, or plasma exchange), tumor removal where applicable, and second-line immunosuppression for refractory cases. Prognosis is strongly tied to how early treatment begins.

b) Capgras Syndrome

Definition and Clinical Presentation
Capgras syndrome is a delusional misidentification syndrome in which a patient believes that a close relative, friend, or sometimes a pet or familiar object has been replaced by an identical-looking impostor. The patient's ability to visually recognize the person is intact, but the accompanying sense of familiarity or emotional connection is absent, leading the patient to conclude the person must be a fake.

Epidemiology
First described in 1923 by Joseph Capgras and Jean Reboul-Lachaux, the syndrome is rare but has been documented across a wide range of underlying conditions: schizophrenia and other primary psychotic disorders, mood disorders with psychotic features, dementia, traumatic brain injury, epilepsy, substance use, and autoimmune encephalitis.

Proposed Neurobiological Mechanism
The leading explanation is the dual-route model of face processing: a cortical, "overt" route that identifies who a face

belongs to, and a separate subcortical route connecting facial recognition areas to the limbic system, generating the automatic feeling of familiarity that normally accompanies recognizing someone we know. In Capgras syndrome, clinicians have argued this case aligns with impaired implicit-affective processing alongside intact conscious recognition- the overt route remains intact while the limbic connection is disrupted.[2]

Diagnostic Criteria and Workup
There is no single diagnostic test for Capgras syndrome itself; it is identified through clinical psychiatric and neurological assessment, with the delusion documented alongside a broader diagnostic workup- neuroimaging, cognitive testing, toxicology screening, and, where autoimmune or infectious encephalitis is suspected, CSF and antibody testing.

Common Misdiagnoses and Why They Happen
Capgras syndrome is most often folded into a diagnosis of the underlying psychiatric disorder it appears alongside- most commonly schizophrenia- without further investigation into whether a specific neurological or organic cause is present.[2] Cases have also been documented as an unrecognized feature of severe depression, substance-induced psychosis, multiple sclerosis, and postpartum psychosis.

Treatment and Prognosis
Treatment follows from the underlying cause: antipsychotic medication where the delusion arises from a primary psychotic or mood disorder, and addressing the underlying substance, autoimmune process, or structural lesion where one is identified.

c) Cotard's Syndrome

Definition and Clinical Presentation
Cotard's syndrome is characterized by nihilistic delusions- the fixed belief that one is dead, does not exist, is decaying, or has lost internal organs or body parts. It exists on a spectrum of severity and is frequently accompanied by severe depression, guilt, and self-neglect or refusal to eat, since a patient convinced they are already dead may see no reason to sustain a body they believe no longer needs sustaining.

Epidemiology
First described by Jules Cotard in the 1880s, the syndrome is rare and most commonly reported in patients with severe or psychotic depression, though it has also been documented in schizophrenia, bipolar disorder, and as a feature of anti-NMDAR encephalitis.[3] Patients typically believe they are dead or have lost their organs or body parts, and the syndrome can appear in patients with depression, schizophrenia, or psychosis caused by an underlying medical condition.[3]

Proposed Neurobiological Mechanism
The leading explanatory framework is a "two-hit" model, related in spirit to the mechanism proposed for Capgras syndrome: a disruption in perceptual-limbic connectivity, followed by a failure to resolve the resulting sense of unfamiliarity through an external explanation- instead, the patient resolves the internal contradiction by concluding that they themselves must not truly exist. A published case report described a patient with confirmed anti-NMDAR encephalitis who developed Cotard's syndrome, noting that an earlier published case had also reported Cotard's syndrome together with Capgras delusion in a patient with the same underlying disease.[3]

Diagnostic Criteria and Workup
As with Capgras syndrome, there is no standalone diagnostic test; Cotard's syndrome is identified clinically and then investigated for an underlying cause, including depression and psychosis assessment, cognitive testing, neuroimaging, and, where indicated, autoimmune antibody panels.

Common Misdiagnoses and Why They Happen
Because nihilistic delusions so often present alongside depression, Cotard's syndrome is frequently absorbed into a diagnosis of psychotic depression or treatment-resistant schizophrenia without triggering a search for an organic cause, particularly in patients with a long psychiatric history.

Treatment and Prognosis
Treatment depends heavily on the underlying cause. Where the syndrome arises from a primary psychiatric illness, antidepressants, antipsychotics, and electroconvulsive therapy have all shown effectiveness. Where an organic or autoimmune cause is identified, treating that underlying process can resolve the delusion directly.

d) Charles Bonnet Syndrome

Definition and Clinical Presentation
Charles Bonnet syndrome (CBS) is characterized by complex, vivid visual hallucinations occurring in people who have experienced partial or complete vision loss, with the critical distinguishing feature that patients retain full insight into the unreal nature of what they are seeing. A published case describes a patient who, two weeks after an occipital lobe stroke, began experiencing visual hallucinations of silhouettes and shapes of people and objects confined to the exact area of his visual loss, while remaining fully aware the images were not real.[4]

Epidemiology
First described in the 18th century by Swiss naturalist Charles Bonnet, CBS is fairly common in populations with significant visual impairment- associated most often with age-related macular degeneration, cataracts, glaucoma, and diabetic retinopathy - and can also follow stroke, brain tumors, or other damage along the visual pathway.

Proposed Neurobiological Mechanism
The leading explanation is a "deafferentation" or "release" model: when visual input to the brain is significantly reduced or lost, the visual cortex becomes hyperexcitable and begins spontaneously generating activity in the absence of normal sensory input. Because the deficit is confined to the visual pathway and does not involve limbic or affective circuitry, the resulting hallucinations carry no delusional interpretation.

Diagnostic Criteria and Workup
Diagnosis is clinical, resting on documented vision loss, complex visual hallucinations, and preserved insight with the absence of delusions or hallucinations in other sensory modalities. Workup centers on ophthalmologic examination

and, where the presentation is atypical, neuroimaging to rule out structural lesions along the visual pathway.[4]

Common Misdiagnoses and Why They Happen

CBS is frequently mistaken for a primary psychotic disorder, particularly in elderly patients, where new hallucinations are often reflexively attributed to dementia-related psychosis rather than investigated as a possible consequence of vision loss. Patient reluctance to disclose the hallucinations, for fear of being labeled mentally ill, likely contributes to underreporting.

Treatment and Prognosis

There is no cure for CBS beyond addressing the underlying vision loss where possible; management centers on reassurance and psychoeducation. Prognosis is generally stable rather than progressive.

4. Comparative Analysis

	Anti-NMDAR Encephalitis	Capgras Syndrome	Cotard's Syndrome	Charles Bonnet Syndrome
Primary symptom domain	Psychosis, seizures, movement abnormalities, autonomic instability	Delusion of impostor replacement	Nihilistic delusion (belief of death/non-existence)	Complex visual hallucinations, insight preserved
Underlying mechanism	Autoimmune antibodies against NMDA receptors, reducing receptor density in hippocampus/forebrain	Disconnection between face-recognition pathway and limbic familiarity signal	Extended disconnection between perceptual/self processing and limbic affective tagging	Deafferentation ("release" phenomenon) from damaged visual pathway
Typical misdiagnosis	Schizophrenia, dissociative disorder, GAD, bipolar disorder with psychosis	Schizophrenia, depression with psychotic features	Psychotic depression, treatment-resistant schizophrenia	Primary psychotic disorder, dementia-related psychosis
Key diagnostic test	CSF/serum anti-NMDAR antibody testing, EEG, tumor screening	No standalone test; workup targets underlying cause	No standalone test; workup targets underlying cause	Clinical criteria + ophthalmologic exam
Insight preserved?	No (impaired during acute phase)	No (fixed delusion)	No (fixed delusion)	Yes (defining feature)
Primary treatment	Immunotherapy (steroids, IVIG, plasma exchange), tumor removal	Treat underlying cause; antipsychotics if psychiatric origin	Antidepressants, antipsychotics, ECT for chronic/refractory cases	Reassurance/psychoeducation; treat underlying cause if identifiable
Prognosis	Good with early immunotherapy; poor if delayed	Variable- depends on reversibility of cause	Variable- ECT often effective in chronic stage	Persists with vision loss but stable, non-progressive

Viewed side by side, these four syndromes resist being treated as an arbitrary grouping of medical curiosities. They form a spectrum, and the table above makes that spectrum visible along two axes in particular: mechanism and preserved insight.

At one end sits anti-NMDAR encephalitis, where the causal chain from cause to symptom is the most direct of the four. At the other end sits Charles Bonnet syndrome, where the mechanism is equally direct but where the resulting symptom carries none of the delusional interpretation seen in the other three- the visual cortex misfires, while the rest of the brain's reality-testing apparatus remains completely undisturbed.

Capgras and Cotard's syndromes occupy the middle of this spectrum. Both are best explained by a disconnection between recognition and the limbic system's affective "tagging" of that recognition — the mechanism differs mainly in scope. In Capgras syndrome the disconnection is narrow, affecting the emotional resonance attached to a specific familiar face; in Cotard's syndrome the same kind of disconnection appears to extend further, touching the patient's sense of their own body and existence. This is not merely a theoretical parallel- it is empirically documented, as the case in which a patient with confirmed anti-NMDAR encephalitis developed Cotard's syndrome referenced an earlier published case in which the same underlying disease produced both Cotard's and Capgras delusions in a single patient.[3] That single data point shows that two syndromes conventionally taught as separate psychiatric diagnoses can emerge from the identical organic disease process, in the same person.

Taken together, the four syndromes suggest a working principle for clinicians: symptoms that look psychiatric sit downstream of mechanisms that range from fully organic and testable to poorly understood, and the symptom alone cannot reliably distinguish which is which. What can distinguish them, more often, is what is happening alongside the symptom: the tempo of onset, the presence or absence of insight, and accompanying findings that fall outside the boundaries of a traditional psychiatric exam altogether.

5. Diagnostic Challenges

Why These Get Misattributed to Primary Psychiatric Disorders

Each case reviewed in this paper shares a common pattern: a patient presents with symptoms that map cleanly onto an existing psychiatric diagnostic category, is treated within that framework, and only receives a neurological workup once the clinical picture develops features that no longer fit. Diagnostic criteria for conditions like schizophrenia and psychotic depression are symptom-based rather than mechanism-based, meaning a patient presenting with psychosis or delusions will, almost by design, meet criteria for a primary psychiatric disorder regardless of the underlying cause.

Red Flags That Should Prompt Neurological Workup

- Acute or subacute onset, particularly in a patient with no prior psychiatric history.
- Autonomic or systemic signs accompanying psychiatric symptoms- fever, abnormal movements, seizures, or unexplained vital sign changes.
- Age or demographic atypicality- new-onset psychosis or delusions far outside the typical range, or in a patient with known vision loss and no psychiatric history.
- Isolated or unusually specific delusional content without the broader symptom picture typically expected of the presumed diagnosis.
- Poor or paradoxical response to standard psychiatric treatment.
- Preserved insight alongside hallucination, which should raise suspicion for a sensory-deafferentation process rather than a primary psychotic disorder.

The Role of Interdisciplinary Collaboration

The cases reviewed throughout this paper share a second common thread beyond delayed diagnosis: the diagnosis, once made correctly, typically required input from more than one specialty. This argues for diagnostic models in which psychiatric presentations are routinely screened for neurological red flags as a matter of protocol, rather than only pursued once a case has clearly failed to respond to standard psychiatric treatment.

The Cost of Delayed or Missed Diagnosis

The stakes of diagnostic delay vary by syndrome but are rarely trivial. In anti-NMDAR encephalitis, delayed immunotherapy is associated with longer illness duration and greater risk of lasting cognitive deficit. In Cotard's syndrome, misdiagnosis prolongs a patient's exposure to real risk of self-neglect and suicide. In Capgras syndrome, an unaddressed underlying cause leaves the actual disease process untreated even while the delusion itself may be sedated into remission. In Charles Bonnet syndrome, misdiagnosis carries a different but still significant cost: unnecessary antipsychotic medication or a wrongly assumed diagnosis of dementia, when what the patient most needs is an accurate explanation of a benign phenomenon.

6. Implications for Clinical Practice

The pattern running through all four syndromes points toward several concrete changes in how psychiatric and neurological presentations are evaluated.

a) Toward Integrated Neuropsychiatric Assessment

A purely symptom-based diagnostic approach is insufficient for a meaningful subset of patients. A more integrated model would build basic neurological screening into standard psychiatric intake: a review for red flags, a baseline neurological exam, and a lower threshold for imaging or antibody testing, particularly for first-episode presentations with no prior psychiatric history.

b) Training Implications

Psychiatry training tends to emphasize symptom recognition and pharmacological management, while neurology training tends to emphasize localization and structural disease; neither curriculum, by itself, adequately prepares clinicians to recognize the four syndromes discussed here. Cross-disciplinary exposure would directly address the diagnostic blind spots illustrated by these cases.

c) Emerging Diagnostic Tools

The growing availability and falling cost of autoimmune antibody panels, along with advances in functional neuroimaging, make it increasingly feasible to screen for organic causes even in patients who present in a purely psychiatric setting. Wider, earlier use of these tools could meaningfully shorten the diagnostic delays documented throughout this paper.

d) A Note on Prognosis-Driven Urgency

Not all four syndromes carry equal diagnostic urgency. Anti-NMDAR encephalitis and Cotard's syndrome both carry meaningful risk of harm if left undiagnosed, making rapid recognition a priority. Charles Bonnet syndrome, by contrast, is benign and non-progressive- its clinical urgency lies in sparing patients unnecessary psychiatric treatment and distress rather than physical risk.

7. Conclusion

The four syndromes examined in this paper- anti-NMDA receptor encephalitis, Capgras syndrome, Cotard's syndrome, and Charles Bonnet syndrome- do not belong in psychiatry or neurology alone. Each occupies a different position along a single continuum, from a fully characterized autoimmune disease that happens to announce itself through psychiatric symptoms, to delusions increasingly explained by specific breakdowns in the circuitry linking recognition to emotion, to a hallucinatory syndrome that leaves the mind's capacity for reality-testing completely untouched. What unites them is not a shared symptom but a shared lesson: the presence of a "psychiatric" symptom says nothing, on its own, about whether its cause is psychiatric.

The case reports reviewed throughout this paper illustrate the real cost of treating that distinction as settled too early- delayed immunotherapy, prolonged psychiatric hospitalization, unnecessary antipsychotic exposure, and in the more severe cases, meaningful risk to the patient's safety. They also illustrate the cost of the reverse assumption: that a psychiatric explanation, once reached, must be final, when in each case reviewed here, a wider diagnostic lens was what ultimately arrived at the truth.

The boundary between neurology and psychiatry was always a product of medical history rather than biological necessity, drawn at a time when the tools to see inside a disrupted brain simply did not exist. As those tools improve, that boundary will likely continue to dissolve- but only if clinicians are trained, and diagnostic systems are structured, to look across it rather than settle on one side. The four syndromes in this paper are a small sample of a much larger category of conditions waiting to be recognized in the same way: not as psychiatric or neurological, but as both, until proven otherwise.

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