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Clinical Commentary

Biological Psychiatry

COVID-19 Catatonia—Would We Even Know?

Joseph J. Cooper and David A. Ross

She was declared dead: After her burial the gravedigger, wishing to purloin her gown, opened the coffin at night; but during this operation, she suddenly returned to life.

—Report by Dr. George Pfendler, 1833 (1)

One of the oldest metaphors, across time and cultures, is being paralyzed by fear: from Lot's wife turning to a pillar of salt (at the horror of Sodom's destruction) to Medusa's victims turning to stone (2). And it's more than metaphor: before widespread use of the stethoscope, mistaking "frozen" catatonic patients as dead and burying them alive was, unfortunately, not uncommon. The woman described above was one such case, buried alive during an attack of "lethargy" and abnormal posturing and saved only by the gravedigger's timely intervention. She became known as *la belle Juive ressuscitée*, the beautiful Jewess brought back to life (1). While we are better today at differentiating life from death, we remain poor at recognizing catatonia.

Despite a remarkably accurate account of its symptoms, signs, and course in 1874 by Kahlbaum, catatonia has been a syndrome lost in the history of medicine (1). Kahlbaum described 26 cases with stuporous, excited, and malignant psychomotor features (Table 1). They suffered from a wide range of illnesses including mood disorders, psychotic disorders, and delirium. Kahlbaum noted that many of these patients had a good prognosis for recovery from their catatonic state, but a subset progressed to a poor, or even lethal, outcome (2).

By the late 1800s, Kraepelin, engaged in his seminal work on psychiatric nosology, introduced his construct of dementia praecox. Despite awareness of Kahlbaum's reports on good outcomes in catatonia, Kraepelin eventually subsumed the concept of catatonia under this broad neurodegenerative syndrome. This error would be repeated for the entire 20th century as catatonia was relegated to a subtype of schizophrenia (1).

The timing was unfortunate. In 1918, shortly after catatonia was buried (alive) under schizophrenia, the world was struck by the so-called Spanish flu. An estimated 500 million people (a third of the world's population) were infected and 50 million died. While influenza's role in this story is well known, catatonia's is less so. Some patients began presenting with profound lethargy and abnormal movements. Constantin von Economo coined the term encephalitis lethargica (EL) to describe this state (3). Months to years later many developed post-encephalitic parkinsonism (PEP), also with prominent catatonic features (3). Since catatonia was defined as a subset of schizophrenia, the relationship between EL, PEP, and Kahlbaum's catatonia didn't occur to most clinicians. EL and PEP patients' illnesses had far too many neurologic features to be considered "schizophrenia," leaving many clinicians baffled.

Because these syndromes appeared to be behavioral, physicians tried to approach them with the psychiatric tools of the time. Smith Ely Jelliffe, a prominent psychoanalyst, psychiatrist, and neurologist, offered this interpretation of oculogyric crises: "symptom formation (i.e., looking away, up, down, sideways) may be… a defensive action to escape anxiety." He offered similar interpretations of EL patients' tremor, sialorrhea, seborrhea, and rigidity as manifestations of psychological and sexual representations, recommending psychoanalysis as treatment (3). Alas, this approach didn't work.

Meanwhile, von Economo was looking for a biological explanation. The mechanism relating EL and PEP to the "Spanish flu" remained a mystery. But von Economo was aware of a similar historical incident, from Italy in 1890, when "nona," a syndrome of stupor and parkinsonism, followed an influenza epidemic (numerous such connections have been historically identified) (3). He had the prescient idea to study their brains.

Von Economo's findings were striking: he found marked destruction in the basal ganglia, midbrain, and hypothalamus, raising the "possibility of organic basis for those apparently functional symptoms…[in the] grey masses at the base of the brain" (3). This revelation—the attribution of psychiatric symptoms to a neurobiological cause—was too far ahead of its time. In an era dominated by psychoanalytic thought, von Economo's revolutionary ideas were discarded and forgotten.

Over the next hundred years, little would change. The world remained free from respiratory pandemic, and psychiatry and neurology failed to incorporate catatonia into mainstream practice. Research emerged in the 1970s and 1980s demonstrating once again that catatonia was a distinct entity, yet most continued to think of it as a subtype of schizophrenia (1). This was problematic. While systematic studies have shown that catatonia is highly prevalent (10% of psychiatric inpatients and 30% of delirious medical inpatients), without having a diagnostic category psychiatrists were literally unable to diagnose it. Accordingly, research showed that only one in nine catatonic psychiatric inpatients were correctly identified as such (4)—a problem compounded by underutilization of the physical exam in psychiatric settings. Catatonia is also routinely missed in neurologic and general medical settings (5), likely driven by unfamiliarity with the syndrome even when individual motor findings are identified. The term "catatonic-like" movements is sometimes seen, reflecting our nosological struggles: if catatonia *is* schizophrenia, then catatonia occurring without schizophrenia is not *real* catatonia.

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Table 1. Historical Diagnostic Categories for Catatonia

Catatonia Symptom Clusters	Kahlbaum (1874)	DSM-5 (2013)
Stuporous		
Mutism	+	+
Lethargy or stupor	+	+
Posturing	+	+
Catalepsy	+	+
Staring	+	
Grimacing	+	+
Waxy flexibility	+	+
Negativism	+	+
Food refusal	+	
Withdrawal	+	
Excited		
Agitation	+	+
Echolalia	+	+
Echopraxia	+	+
Motor repetition	+	+
Verbigeration	+	
Automatic obedience		
Rapid alternation		
Malignant		
Hyperthermia	+/−	
Hyperautonomia	+/−	
Confusion	+/−	
Rigidity		
Muscle breakdown		

Catatonia is a neurobiological state that existed before we had a name for it, and will continue to exist, regardless of what we decide to call it. Catatonia symptom clusters are on the left-hand column. Kahlbaum's original description included most catatonic features, but he is generally not credited with describing the malignant form. Progression to lethal outcomes in Kahlbaum's series may have been due to worsening underlying medical disorders. Following Kahlbaum, catatonia was only diagnosable as a subtype of schizophrenia; thus, the vast majority of 20th century catatonia was undiagnosable. The DSM-5 saw the abolition of the catatonic subtype of schizophrenia, and the diagnosis of catatonia covers much more of the true spectrum of catatonic symptoms. Yet, it remains incomplete, particularly in its exclusion of malignant features and catatonia presenting with delirium.

Catatonia is sometimes only identified after it is too late and serious complications have emerged: dehydration, aspiration, pressure ulcers, pulmonary emboli, or progression to malignant features. One of the most dangerous sequelae may be iatrogenic: when clinicians prescribe dopamine antagonists and inadvertently provoke the malignant form of catatonia known as the neuroleptic malignant syndrome (2). The vast majority of this morbidity and mortality is readily avoidable—nearly all cases will respond to treatment with benzodiazepines and/or electroconvulsive therapy (ECT) (1,2).

These clinical observations led to two crucial advances in understanding the biology of catatonia: the efficacy of benzodiazepines implicated the GABAergic system, and the role of dopamine antagonism implicated the basal ganglia [the "grey masses at the base of the brain" (3)] (2).

Modern neurology would help inform a third piece of the puzzle. In 2007, Josep Dalmau described a case series of women with a paraneoplastic syndrome that included subacute-onset psychiatric and "catatonic-like" motor features. The work offered the first description of anti-NMDA receptor encephalitis (6)—which is now recognized as the most common form of autoimmune encephalitis. Moreover, the link to catatonia—and, thereby, the role of glutamatergic signaling—is clear and consistent: 70.6% of these patients have catatonia (7).

Together, these data demonstrate that there is not a single answer to what causes catatonia. Dysfunction of cortical-subcortical motor regulation systems—involving GABA, dopamine, and glutamate—may constitute a biological vulnerability (2). There may also be value in the original metaphor: fear may induce a heightened and prolonged sympathetic freeze response in at-risk individuals (2). These need not be mutually exclusive—rather, they may each represent varied entry points into the catatonic state. By analogy, consider ARDS (acute respiratory distress syndrome). ARDS has many possible causes—from infection to pancreatitis to drug toxicity—that all lead to dyspnea, hypoxemia, and diffuse pulmonary opacities. It is crucial to treat both the emergent state (i.e., to provide respiratory support) *and* the underlying cause (e.g., prescribing antibiotics for bacterial pneumonia). Similarly, catatonia is an emergent state requiring acute treatment (i.e., benzodiazepines and ECT) *and* a simultaneous search for contributing factors (1,2).

One major historical lesson is clear: if you don't know to look for catatonia, you won't find it. We are in the midst of a new global pandemic, unprecedented in any of our medical careers. Appropriately, the initial focus is on respiratory emergencies. But the secondary fallout is emerging—cardiovascular, inflammatory, and neuropsychiatric. The potential neuropsychiatric mechanisms of COVID-19 are many (8): from direct viral encephalitis to cytokine dysregulation, immune cell transmigration, postinfectious autoimmunity, effects of immunomodulatory treatments, hypoxic brain injury, and posttraumatic stress from a near-suffocation event compounded by required social isolation. The resultant neuropsychiatric presentations will surely have varied features.

Will they include COVID-19 catatonia? If history is any indication, we have reason to be concerned. An early case report from Italy described respiratory COVID-19 progressing to irritability, confusion, asthenia, and then to "akinetic mutism" (9). What we call things matters. Akinetic mutism is a neurologic state of alertness without speech or movement, classically caused by irreversible medial prefrontal or midbrain damage. However, it is often a mistaken label given to patients with treatable stuporous catatonia (1,2), especially when no causative lesion is identified. This report, along with nearly all neurologic COVID-19 case series, makes no specific mention of catatonia. Yet there is also room for hope: a recent paper on delirium in COVID-19 highlights the overlap and differences between catatonia and akinetic mutism, reinforcing the importance of accurate diagnosis (10).

Our collective awareness of catatonia must be resuscitated. With an index of suspicion, we can perform a motor exam and

identify a treatable syndrome across diverse medical settings. In the time of the "Spanish flu," EL, and PEP, even these steps would not have improved outcomes; sodium amytal and chemical convulsive therapy, the predecessors of today's benzodiazepines and ECT, were still a decade away (1). Today, while our patients will not be literally buried alive, the story of *la belle Juive ressuscitée* remains a stark reminder of the cost of untreated catatonia.

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Article Information

From the Department of Psychiatry (JJC), University of Illinois at Chicago, Chicago, Illinois, and the Department of Psychiatry (DAR), Yale University School of Medicine, New Haven, Connecticut.

Address correspondence to Joseph J. Cooper, M.D., Department of Psychiatry, University of Illinois at Chicago, 912 S Wood St (MC 913), Chicago, IL 60612; E-mail: cooperj@uic.edu.

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