

Time-of-Day and State-Dependent Variation in Movement Disorders: A Primer of Relevant Clinical Conditions

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Abstract

Movement disorders may vary with the time of day and with mental state. Despite hypothalamic control of biological timing, we discuss how many cell populations throughout the brain and body, including dopaminergic nuclei, likely have time-keeping functions. We provide a “primer” of movement disorders with significant variation in time or with presentation in a state of altered consciousness. Parkinsonism illustrates our overall argument. Patients with an idiopathic behavioral and motoric disorder in sleep develop a parkinsonism eventually, at a high phenotype conversion rate over roughly ten years. Diurnal variation in severity of motor manifestations happens after diagnosis of a parkinsonism, and nocturnal movements of various types also occur after diagnosis. An inflammatory or autoimmune mechanism for timing or state variability in movement disorders may be part of the pathophysiology in many Parkinsonisms, but autoimmunity as a disease mechanism becomes particularly relevant in various encephalitides associated with movement disorders. We address seven major syndromes. Further addressing temporal variability, we then discuss Willis-Ekbom (restless legs) syndrome, an akathisia that implicates both iron and dopamine. Clinically, it is a multi-faceted movement disorder associated with either recumbency or with sleep. Next, we discuss dystonias characterized specifically by variation during the day. The clinical implications of our review are several: Parkinsonism is not exclusively a motor disease; identification of movement disorders is increasingly important in encephalitic conditions; state-dependency (in altered consciousness, in repose, in sleep) and temporal variation are hallmarks of many dyskinesias. We end with observations about the relevance of time in the assessment of disordered movement.

Keywords: Diurnal, Circadian, Parkinsonism, Synucleinopathy, Surface and cytosolic antibodies, Restless legs, Dopamine, Monogenic dystonia

Introduction

Clinicians are familiar with a question they should routinely ask of patients: are there factors that elicit or exacerbate a problem? In movement disorders, a relevant question might be: is there a time of day when a motor problem (a dyskinesia, such as restlessness or akathisia) occurs especially? It is a truism that many movement disorders, with the exception perhaps of myoclonus, lessen or dissipate during sleep [1]. Yet

dyskinesias may manifest at different times in a day, in sleep, or in a state of altered consciousness. We examine the variety of conditions in which time-of-day or state-associated motor manifestations matter in reaching a correct diagnosis.

Our interest in movement disorders in the time domain stems from past studies, reviewed in [2], that explore how planned and spontaneous movements and transitions in behavior may involve dopamine neurons (DANs) as time

keepers. In animal studies, DAN firing modulates a propensity to movement; the firing does not trigger movement *per se* [2]. In humans, the appearance of adventitious movements related to time of day, to wakefulness or sleep, or to an altered state of consciousness invites consideration of a role that dopamine (DA) or other mechanisms might play in generating such time-associated propensity to movement or dyskinesia. Disrupted circadian rhythms have been described in Parkinson disease (PD) and other neurodegenerations [3-6], and some treatments specifically target circadian disruption [7]. But timing issues are not specific to neurodegenerative disease. A number of contemporary reviews examine motor symptoms in encephalitic syndromes with neural antibodies [8], the complex relationship between restlessness and DA [9], and dystonias characterized by diurnal variation and response to levodopa [10].

We feel that a single review would help to summarize entities that have been described in the past more or less individually. We offer a primer of practical, clinical basics regarding time- or state-dependent movement disorders. Although we attempt thoroughness, we do not claim to provide systematic reviews of the diseases we discuss. Our choice of citations involved

different search strategies, depending on the disease category. For the antibody-mediated syndromes and for Willis-Ekbom (restless legs) syndrome, we consulted comprehensive reviews with the intention specifically to revisit original citations, and to highlight clinical and laboratory details not always provided in reviews. In other sections of this paper, we adopted more traditional, search-engine based reviews of the literature. We describe our search strategies in the “**Supplementary Material**” to this paper.

General Considerations from Chronobiology

Neuronal activity varies across light-dark cycles, particularly among the 10-20,000 specialized neurons of the paired suprachiasmatic nucleus (SCN) of hypothalamus [11-13]. SCN is considered the dominant circadian pacemaker in mammals. As the name indicates, it is located above the optic chiasm in anterior hypothalamus. Its neurons oscillate their resting membrane potentials and their firing rates, both of which are coupled to a 24-hour transcriptional-translational feedback loop, whose genes and associated proteins (e.g., Clock [Circadian Locomotor Output Cycles Kaput], Period1 [Per1], among many others; see **Figure 1**) have been studied in

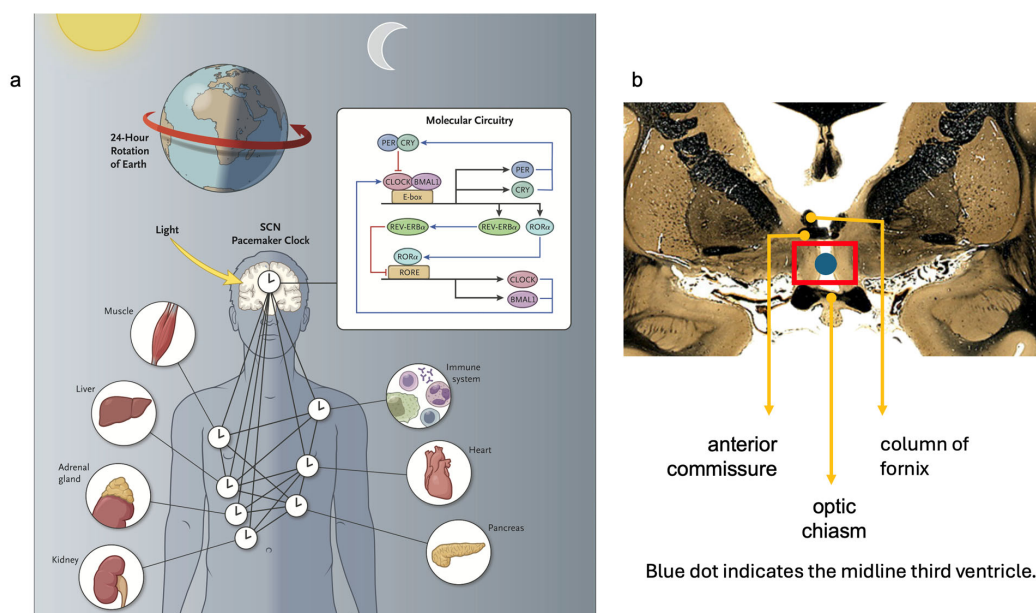


Figure 1. Some locations of biological clocks. **1a.** The inset summarizes translational and transcriptional loops that operate in suprachiasmatic nucleus (SCN) of hypothalamus. PER: Period (clock repressor); CRY: Cryptochrome (clock repressor); CLOCK: Circadian Locomotor Output Cycles Kaput (core clock loop); BMAL1: Brain and Muscle “Arnt”-like Protein 1 (core clock loop); E-box: Enhancer Box; REV-ERB alpha: Member of Superfamily of Intracellular Transcription Factors; ROR: Retinoic Acid-Related Orphan Receptor (reinforces loop activity); RORE: ROR Response Element. Note that not all “peripheral” clocks in the body or elsewhere in the brain (other than in hypothalamus) need to be synchronized with the SCN “master” clock. Figure from Allada and Bass (11), © 2021 Massachusetts Medical Society, with permission.

1b. Paired SCN(s) are located in the preoptic area of anterior hypothalamus (inside the red box), inferior to both the columns of the fornix and the anterior commissure and superior to the optic chiasm. A column of fornix, the midline anterior commissure, and the optic chiasm are indicated by orange arrows. The blue dot sits in the cavity of the third ventricle. Coronal image of brain (fiber tracts stain darkly): courtesy of the National Museum of Health and Medicine, Michigan State University and the University of Wisconsin, available online at <http://brainmuseum.org>. The anatomical collections are supported by the National Science Foundation and the National Institutes of Health, and are in the public domain.

detail [12]. The view that SCN drives all circadian periodicities, however, has been challenged, based on observations that *Per1* (*inter alia*) is expressed variously throughout the brain, that extra-SCN sites can manifest their own firing rhythms, and that multiple brain oscillators (or “clocks,” not referring to the “Clock” gene) contribute significantly to the control of physiological systems [11-14].

Animal studies find that age (three months *versus* 24 months in normal mice) adds another consideration. In old mice, SCN neurons fire increasingly out of phase with each other when compared to young mice, although SCN neurons retain overall differences in oscillation between light and dark intervals of a day [15]. SCN is a dominant pacemaker, but not the only one in the brain, and the coherence of its neuronal firing varies over a lifetime. Furthermore, brain clocks like SCN differ from so-called “peripheral” clocks, which are present in cells throughout the body, and which govern diverse metabolic processes which themselves vary both over 24 hours and with age [11-14].

Even a cursory view of a rich chronobiological literature raises issues that frankly blur when we consider the time of day of neurological signs and symptoms. For example, “sundowning” colloquially refers to disruptive behavior during a transition in a 24-hour cycle [16]. But there is no consensus definition of the sundowning phenomenon [17]. Seeking cause for a change linked to time of day introduces a surfeit of possibilities that may coexist. Some major considerations, detailed in **Table 1**, speak to a widely accepted notion that there are many biological clocks and many ways by which those clocks, in both brain and body, can mis-time.

Returning to the idea of a dominant pacer: overall, light and dark difference tracks with motorically active and rest periodicity. If normal movement varies over a day, can we describe time dependency in movement disorders?

Time-of-Day Studies in Parkinsonism

Even before the development of motor signs, is there already a disturbance in cycles of activity and rest in Parkinsonism?

A behavioral disorder that manifests during rapid-eye-movement (REM) sleep is well known to be a herald of alpha-synucleinopathies, especially idiopathic Parkinson disease

(PD), before the appearance of classical motor features of bradykinesia, rigidity, and tremor, or combinations of those three signs [18-20]. A phenoconversion rate from the polysomnographic diagnosis of an idiopathic REM-sleep behavior disorder (RBD) to an overt neurodegenerative syndrome (PD, dementia with Lewy bodies [DLB], multiple system atrophy [MSA]) has been quoted at roughly six percent per year, with overall ~75% conversion after 12 years [18].

Antelmi *et al.* [21] invoke criteria for diagnosis from the International Classification of Sleep Disorders, third edition: importantly, RBD requires polysomnographic demonstration of loss of muscle atonia during REM.

REM *without* atonia (RWA) is a kind of hyperkinesia, since muscle atonia is physiologic in REM. The absence of atonia in RWA is pathological by definition. Actigraphy, which enlists a watch-like action sensor worn at the wrist or ankle or both, is used in evaluations by sleep specialists, but video polysomnography remains the gold standard for evaluation of RWA. The value of Antelmi *et al.*’s review is its attention to a long list of idiopathic RBD mimics, some discussed later in this paper, but RBD in obstructive sleep apnea is especially common. As noted, idiopathic RBD carries high predictive value for an ensuing synucleinopathy, so exclusion of mimics has prognostic significance with implications for disease modifying interventions to mitigate progression in a parkinsonism.

Dream enactment in RWA, despite a connotation of dramatic action, can be subtle, and scoring of RWA relies on such nuances, which need not manifest during all REM epochs, and which can be very brief (e.g., three seconds in duration) [21]. Movements include tonic or phasic muscle activity of the chin (mentalis or submentalis muscle) and phasic activity of flexor digitorum superficialis (action of which involves flexion of the index finger through pinkie at the proximal interphalangeal joints) [22].

RBD antedates and commonly coexists with clinical Parkinsonism—in 60% of PD patients and in 80-100% of those with either DLB or MSA [23]. RBD may predict “malignant” forms of Parkinsonism characterized by more severe cognitive sequelae [24]. EMG phasic activity occurs only in REM sleep in RBD, consistent with absence of atonia in RWA [23]. We emphasize, however, that such EMG signatures offer only a snapshot of what can be far more striking movements in RBD.

Table 1. Selected factors that influence biological timing.	
Factor	Example
Misalignment between SCN firing and the environment	Night-shift work; travel across multiple time zones
Misalignment between SCN as master clock and other brain or peripheral clocks	See "Time-of-day studies in Parkinsonism," above: disturbance of temporal cycles of activity and rest
Exogenous or iatrogenic factors	Use of psychotropic medications, e.g. for "sundowning"
Circadian disruption promoting pathogenesis in distinct organs of the body	Attenuated response to oxidative stress with consequent further disorganization of time perception [6,13]

The compelling observation of a parkinsonian prodrome specifically in sleep invites questions regarding pathophysiology in RWA and idiopathic RBD. Is DA deficiency or alpha-synuclein or both involved? A related question pertains to what is known in the time domain *after* parkinsonism manifests its hallmark clinical signs.

Does PD vary diurnally?

In a cross-sectional study of untreated (*de novo*) PD patients, van Wamelen *et al.* [25] evaluated 174 subjects from 7 a.m.-10 a.m., 181 from 10 a.m.-1 p.m., and 63 from 1 p.m. to 6 p.m. Using the Movement Disorders Society United Parkinson's Disease Rating Scale, part III (MDS-UPDRS III), the authors found statistically significant worsening over that abbreviated day (7 a.m.-6 p.m.), especially in bradykinesia. The concern about *de novo* status pertains to the potential confound of any PD treatment, since both DA loss and dopaminergic treatment may affect endogenous timing mechanisms, in accord with an observation mentioned earlier, that DA neuronal firing constitutes a non-SCN clock [2]. Patients were almost exclusively in Hoehn and Yahr stages one and two (HY1, 2), viz., with either unilateral (HY1) or bilateral (HY2) signs without postural abnormality. Their MDS-UPDRS III scores varied from medians of 18 to 20 to 23 for the three consecutive time epochs, respectively. All the medians are relatively low, indicating mild-to-moderate motor impairment. An attempt to corroborate those data longitudinally in a smaller cohort (27 readouts in 12 subjects, who wore motion sensors until 9 p.m.), found worsening of bradykinesia from 9 a.m. to 9 p.m. When we compare van Wamelen *et al.*'s findings to an earlier, controlled investigation [26], variation also happens in age-matched controls, but the overall difference between the most and least active times of day was greater for controls than for patients, including those with advanced PD (HY3-5).

We conducted a targeted literature review to address what has otherwise been reported regarding daytime and nighttime variability in PD and, especially, PD manifestations at night (see "**Supplementary Material**" for our method). Treated PD patients have been studied using novel techniques, including smartphone and other actigraphy technology [27-29] and analysis of gait initiation disturbances [26]. Those studies report reduced amplitude of rest *versus* active time epochs in a day, and the findings have been corroborated in other studies of both *de novo* and advanced PD [reviewed in 4 and 30-32].

Nocturnal movements in Parkinsonism

Loss in the amplitude of difference between more and less active time epochs in a waking day does not speak to motor manifestations in sleep. Nor did our preceding discussion of RBD/RWA address what has been otherwise reported specifically at nighttime in PD.

Two thirds to nearly 100% of PD patients report insomnia [33,34]. Given the ubiquity of the problem, questions arise

about what causes sleeplessness in PD, as multiple rating scales try to ascertain and to quantify [33,35]. An "insomnia syndrome" relates to difficulty falling asleep, awakening during the night, early awakening, and associated daytime fatigue related to lack of restful sleep. These syndromal criteria keep company with each other [36]. Specifically in terms of motor manifestations under the broad rubric of "tossing and turning," Mirelman *et al.* [34] observe that overall "nocturnal lying time" (first >60 minutes supine to last 60 minutes supine) does *not* differ between patients and controls, but fragmentation of rest (greater upright time during the night) occurred in PD patients, with greater upright time associated with increasing PD severity.

Transition from a supine to upright position differs from restlessness in recumbency and movement disorders of sleep or resting wakefulness [36]. We discuss restless legs in a separate section dedicated to the Willis-Ekbom syndrome, below. Here we draw attention to restlessness and nocturnal movement specifically in PD. The restlessness, typically but not exclusively in the legs, is not the result of myalgia, cramping, venous insufficiency or other etiologies. Zhu *et al.* [37] and Matsubara *et al.* [38] interviewed a total of 325 PD patients to find that an urge to move with or without actual movement occurs in PD (when patients are supine but awake), sometimes with asymmetry (restlessness greater on the side first afflicted, since presentation in PD is characteristically asymmetrical). Although Matsubara *et al.* found that bilateral symptoms were more common, other studies [39-41] corroborate PD-like asymmetry. Neither Zhu *et al.* nor Matsubara *et al.* speak in detail about the nature of leg movements when they occurred ("walking" and "stretching" are mentioned).

Yet very specific motor phenomena have been described, including periodic leg movements of sleep (PLMS) and periodic leg movements of resting wakefulness (PLMW) [33,42]. The movements are involuntary and stereotyped: dorsal extension of a big toe together with partial flexion at the ankle, knee, and sometimes the hip; movements last from 0.5-10 secs with a run of at least four movements with variable inter-movement intervals, up to 90 secs [43]. We discuss PLMS and PLMW in greater detail in our discussion of Willis-Ekbom syndrome, below.

Studies in timing disruption in Parkinsonism

RBD is more likely in MSA or DLB than in PD—to which we can add that RBD is rare in Alzheimer disease (AD), uncommon in Huntington disease (HD), and also rare in most tauopathies except for a Guadeloupean tauopathy with features of a progressive supranuclear palsy (Gd-PSP) [23,44]. Once clinically diagnosed with a parkinsonism, sleep-associated motor manifestations—either RBD, PLMS/PLMW, or both—do not regress [23,43]. Can one localize a lesion or the lesions specifically responsible for the loss of atonia, the elaboration of RBD, or for the specific phenomenology of PLMS/PLMW in conditions associated with DA deficiency?

Nollet *et al.* [45] and French *et al.* [46] emphasize the redundancy of circuits involved in sleep-wake regulation, despite a “master” timekeeper (SCN of hypothalamus). Specific to DA, one anatomical approach is to think about where DA neurons (DANs) are in the brain. French *et al.* [46] discuss dopaminergic amacrine cells of retinas which input directly to SCN. Li *et al.* [47] and French *et al.* [46] discuss how SCN circadian genes and their protein products (e.g., Clock) both modulate and are modulated by DANs: 1. Clock gene expression directly affects both the rate-limiting enzyme for DA synthesis (tyrosine hydroxylase) and, therefore, DA metabolism at the level of the corpus striatum; 2. circadian genes effect DAN activity at the midbrain ventral tegmental area (VTA) probably by a post-translational mechanism; and 3. DA itself regulates Clock function in SCN. Nollet *et al.* [45] further describe how VTA in mice contributes to the generation of both non-REM and REM sleep, by way of differing projects of VTA DANs—for example, a VTA projection to basolateral amygdala in the generation of REM sleep, as was reported in 2022 [48].

Contemplating cell loss in PD—a neurodegeneration not restricted to DA nuclei—Mariotti *et al.* [49] argue that early involvement of locus ceruleus (LC), a catecholaminergic nucleus which perhaps degenerates before DAN nuclei, may specifically be responsible for RBD in PD. Rathor and Ch [50] observe that, although circadian disturbance occurs in genetic parkinsonisms in *Drosophila*, overexpression of alpha-synuclein has not been consistently associated with circadian disturbance. French *et al.* [46], however, convincingly argue that several brainstem and diencephalic nuclei—including brainstem locales associated with the ascending reticular activating system and orexin-producing cells of hypothalamus—are likely also involved in the evolution of sleep-related phenomena in Parkinsonism.

Various dopamine related mechanisms related to timing disturbances are summarized in **Table 2**.

Neuroinflammation as causal?

Localization, as the above brief summary suggests, is not straightforward. The difficulty augments when we consider a striking thought offered by Li *et al.* [47]. The authors are not sure that circadian or other temporal disruption is necessarily the consequence of progression in PD, because circadian

disruption may itself *cause or exacerbate* PD pathophysiology, as a result of neuroinflammation under non-SCN control in brain microglia [see also 50-52]. An inflammatory mechanism for sleep disturbance and motoric manifestations has precedent in autoimmunity associated with narcolepsy type 1 (autoimmune targeting of orexin containing neurons) [53].

We now turn our attention to well-characterized, antibody-associated syndromes in which disturbed consciousness or a sleep abnormality occurs or may eventually manifest in concert with a movement disorder. After our discussion of antibody-syndromes, we address Willis-Ekbom (restless legs) syndrome and selected dystonias with time-of-day manifestations which define them.

State (Sleep)-Related Movement Disorders in Antibody-Associated Disease: Major Examples

As we have seen, the Parkinsonisms exhibit disturbances in sleep. In a state of altered consciousness, as in an encephalitis, what non-Parkinsonian movement disorders are important to notice?

The movement disorder, if appreciated, clues one to diseases for which early diagnosis is vital. Early therapeutic intervention based on prompt diagnosis of antibody-associated encephalitic disease increases the likelihood of favorable outcomes. In this section, we address seven major antibody-associated encephalitides. **Table 3** summarizes red flags for these disorders as well as laboratory correlations.

While excellent reviews have been published on the general topic of these entities [54,55], we focus on aspects at the intersection of abnormal sleep and movement, based primarily on first reports of a given syndrome.

Anti-IgLON5 (Immunoglobulin like, superfamily of five cell adhesion molecules, including limbic system-associated membrane protein, opiate-binding cell adhesion molecule, neuronal growth regulator 1, neurotrimin, and “IgLON”5) [56], antigen at plasma membrane

In Sabater *et al.*’s [57] 2014 report of eight patients, the authors reproduced detailed polysomnography for patient one, their index case, who was a 59-year-old man who

Table 2. Dopamine (DA) and SCN interactions (see text for discussion and references)	
Input from external world to SCN	Amacrine cells of retina (altered transmission of environmental light)
SCN and DA synthesis	SCN gene expression regulates DA synthesis by action at rate-limiting enzymes of DA synthesis
SCN and DA projections	Post-translational effects: demonstrated, in particular, for ventral tegmental area of midbrain (a DA nucleus) and its projections to amygdala and corpus striatum
DA effects on SCN	DA itself regulates CLOCK (Circadian Locomotor Output Cycles Kaput) gene expression
A role for neuroinflammation	Microglial activation in Parkinsonism contributing to disturbed DA synthesis and abnormal SCN-DA interaction

Table 3. Summary of relevant antibody syndromes.		
Antibody mediated syndrome	Red flag signs/symptoms	Typical diagnostic findings
Anti-IgLON5	RBD, gait-predominant parkinsonism and supranuclear gaze palsy, bulbar symptoms, dementia with craniofacial dyskinesia	MRI: typically nonspecific [66]; some reports of diffusion restriction in high pontine tegmentum, dorsal midbrain, deep cerebellar white matter, superior cerebellar peduncles, and thalamus [67,68]; T2 hyperintensities can be seen in hypothalamus and tegmentum [69]
		EEG: nonspecific [66]
		CSF: cell count <10, total protein elevation (median 86mg/dL) [63,70]
Anti-NMDAR	Adults: Acute psychiatric changes, seizures, mouth and arm dyskinesias that persist in sleep. Antecedent HSV encephalitis [74]. Children: acute psychiatric changes, new insomnia, decreased level of consciousness, orofacial dyskinesias [86].	MRI: Findings not part of extant diagnostic criteria, but FLAIR changes have been seen in medial temporal lobes, basal ganglia, cerebellum, brainstem, hypothalamus, corpus callosum, and other nonspecific regions [76]. Atrophy can be seen in post-recovery phase [85].
		EEG: focal or diffuse slowing, disorganized activity, “delta brush” [82]
		CSF: mild pleocytosis is common, range is high [77,83]; total protein can be elevated [76]; oligoclonal bands are common but may require multiple samples [83]
Anti-CASPR2	Peripheral nerve hyperexcitability; fibrillary chorea; severe refractory insomnia with dysautonomia, seizures, encephalopathy, <i>agrypnia excitata</i> , RWA. Insidious development over months [88,89].	MRI: normal in 70% [94]
		EEG: epileptiform discharges, slowing [94], abnormal sleep including absent non-REM sleep architecture [93]
		CSF: normal in up to 65% of cases, can see mild pleocytosis or protein elevation [94]
		Other: EMG shows peripheral hyperexcitability [89,93,94]
Anti-LGI1	Faciobrachial dystonic seizures (FBDS) [99-103], encephalopathy, amnesia, RBD with encephalitis, any combination of the above with concurrent hyponatremia	MRI: medial temporal lobe FLAIR hyperintensities [92,93]
		EEG: epileptiform discharges, focal slowing in FBDS [99-103]
		CSF: typically normal, can have mild pleocytosis [98]
		Other: serum hyponatremia [99-103]
Anti-Ma2	Hypothalamic/diencephalic dysfunction, limbic encephalitis, brainstem encephalitis, excessive daytime sleepiness with cataplexy, RBD with parkinsonism and vertical gaze palsy and/or apraxia of eyelid opening, RWA [80,107-110]	MRI: FLAIR hyperintensities in medial temporal lobes and multiple subcortical regions have been described (thalamus to medulla) [108]
		EEG: abnormal sleep architecture [109]
		CSF: mild to moderate pleocytosis (5-113 cells/ μ liter), mild to moderate protein elevation (47-747mg/dL), reduced hypocretin levels [111]
		Other: commonly associated with cancer, including: lung, GI, breast, kidney, lymphoma, melanoma [105].
Anti-DPPX	Classic triad: Weight loss with diarrhea, cognitive dysfunction, CNS hyperexcitability (exaggerated startle, myoclonus, seizures); PLMS, RBD, OSA, <i>agrypnia excitata</i> [112-115]	MRI: normal or nonspecific [112]
		EEG: abnormal sleep architecture; report of simultaneous REM and non-REM architecture [114]
		CSF: mild to moderate pleocytosis (11-117 cells/ μ liter), mild protein elevation (up to 82 mg/dL) [112]

Anti-GABA _B R	New seizures, memory changes, behavioral abnormalities, excessive sleep or insomnia; one description of reduced REM sleep, fluctuating bulbar syndrome, and <i>agrypnia excitata</i> [116-123]	MRI: FLAIR hyperintensities in medial temporal lobes [120]
		EEG: normal or nonspecific
		CSF: mild to severe pleocytosis (0-950 cells/μliter) and mild to moderate protein elevation (35-109 mg/dL)
		Other: SCLC, other autoantibodies can be seen. Among those with SCLC – anti-SOX, anti-amphiphysin, anti-Hu/ANNA1, anti-Ri/ANNA2. Among those without SCLC – anti-GAD, anti-NMDAR, anti-IgLON5 [120-123].
We summarize relevant antibody-mediated syndromes with red flags and typical diagnostic findings. Note the concurrence of sleep and movement disorders and overlap between the syndromes. Different antibodies may lead to similar dysfunction of cortical and subcortical structures.		
CSF: Cerebrospinal Fluid; CNS: Central Nervous System; EEG: Electroencephalogram; EMG: Electromyogram; FLAIR: Fluid-attenuated Inversion Recovery; GI: Gastrointestinal; HSV: Herpes Simplex Virus; MRI: Magnetic Resonance Imaging; OSA: Obstructive Sleep Apnea; PLMS: Periodic Limb Movements Of Sleep; RBD: Rapid-Eye-Movement (REM) Sleep Behavior Disorder; SCLC: Small-Cell Lung Cancer		

presented with abnormal sleep behaviors, sleep apnea, stridor, hypersalivation, excessive sweating, and episodic but “intense” daytime sleepiness—all in the absence of dementia, parkinsonism, gaze palsy, gait disorder, ataxia, or daytime dyskinesia. Motor events occurred in REM sleep, “poorly structured” stage-two non-REM sleep, and in “undifferentiated” non-REM epochs (irregular theta, no vertex waves, K complexes, sleep spindles, or delta slowing). RBD was present based on recording of submentalis muscle and limb movements during REM sleep. In both REM and non-REM sleep, simple and complex vocalizations, jerks of multiple muscles at a time, kicking (although the leg movements did not meet criteria for PLMS), punching, and “finalistic” movements, which resembled identifiable activities such as eating or the manipulation of objects, were observed.

After obtaining cerebrospinal fluid (CSF) and serum, immunohistochemistry on sections of rat brain and cultured neurons identified an antibody to a cell-surface protein later determined to be IgLON5, based on study of transfected human epithelial kidney (HEK) cells. Given known human leucocyte antigen (HLA) associations with autoimmune disease generally, the authors pursued genotyping. Patient one and three others had HLA-DQB*05:01 and HLA-DRB1*10:01 alleles. Neuropathology in two patients (not patient one) found tau collections beyond what is seen in normal aging in hypothalamus, prehypothalamic area, and brainstem tegmentum (laterodorsal tegmentum, periaqueductal grey, pedunculopontine nucleus, magnocellular nucleus, and nucleus ambiguus).

Among the eight patients reported in 2014, four presented with a sleep disorder (one of whom had central hypoventilation) and four with non-parkinsonian gait instability (three of whom had central hypoventilation). Two of the latter four developed sleep-associated movements after the gait disturbance. All those with central hypoventilation died. Subsequent publications have elaborated a wide spectrum of presentations in anti-IgLON5 [58-70].

Gaig *et al.*’s [58] four fundamental clinical profiles help to organize the variability. At onset, anti-IgLON5 may manifest as 1.) a movement disorder in sleep, as in patient one, above; 2.) a bulbar syndrome that can resemble myasthenia gravis or motor neuron disease [64]; 3.) a gait disturbance (unsteadiness/imbalance, a feeling of lateropulsion or retropulsion), sometimes with vertical gaze palsies that might lead one to think about progressive supranuclear palsy (PSP, in which RBD is not at all common), but axial stiffness and rigidity presents only in ~25% [60]; and 4.) a cognitive disturbance with hyperkinesias (craniofacial movements commonly). For the last three, sleep disorders may evolve later in a patient’s course. Relationship to concomitant or antecedent infection (e.g., Epstein-Barr virus) is “plausible” [62], but has not been studied systematically. Cancer associations have been reported in up to 15%, but the discovery of tumors may be coincidental, based on diagnostic criteria for a paraneoplastic neurologic syndrome [65]. Standardized evaluation for malignancy was not part of one study (n = 20) in which breast adenocarcinoma in one patient was diagnosed prospectively [59].

Anti-IgLON5 treatment experience: Grüter *et al.* [63] distinguish between short-term immunotherapy (single courses of intravenous immunoglobulin (IVIg), IV steroids, or plasmapheresis [PLEX]) vs. long-term/long-acting immunotherapy (azathioprine, rituximab, pulsed cyclophosphamide, repetitive IVIg, relapse-independent use of steroids, or repetitive PLEX). In their retrospective review of 53 patients, early initiation of short-term therapy (less than six weeks after diagnosis) resulted in physician-judged improvement. Long-term therapy resulted in response up to 75%. Serum or CSF anti-IgLON5 titers rose with increasing time after diagnosis, despite treatments. Mortality, often due to respiratory complications, reached 19% after three years.

Pathophysiologic questions raised by anti-IgLON5: As Giannoccaro *et al.* have discussed [71], anti-IgLON5 specifically raises mechanistic questions at the interface of neuroimmunology and neurodegeneration. We summarize

such questions (and answers) in **Table 4**. Regarding other antibody syndromes, answers are less clear, due to variability in reports or lack of information to date.

Anti-NMDAR (N-methyl-D-aspartate—NR1 and NR2 subunits—receptor), antigen at plasma membrane

Since its discovery, anti-NMDAR has become recognized as the most common non-viral encephalitis [72-86]. Nine young women reported by Vitaliani *et al.* all had ovarian teratomas 74). Armangué *et al.* [75] describe that antecedent herpes simplex virus (type 1) encephalitis (HSVE) may trigger anti-NMDAR. Progression in anti-NMDAR is common. In adults, psychiatric symptoms happen early. A decreased level of consciousness and dysautonomia happen later [76-78]. Female predominance has been confirmed in multiple studies [72,78]. Children are more likely to present with irritability, insomnia, abnormal movements, and seizures, while adults tend to present with psychosis, and are more likely to develop hypoventilation [72,78,79].

A common anti-NMDAR sleep disturbance is insomnia with daytime hypersomnolence [76,80]. What has been described as *status dissociatus/agrypnia excitata* (to be discussed in greater detail with respect to anti-CASPR2, below) may present with complex movements (antigravity in the arms especially, as well as perioral dyskinesia) which can be evoked with sensory stimulation, and which occur in “a state of paradoxical

and alternating responsiveness [81].” Dream enactment and disorders of arousal (“confusional arousals and somniloquy”) occur, as does RWA [76,80]. Sleep disturbances can persist despite treatment. Interestingly, the hypoventilation that is a hallmark of more advanced encephalitis is not always associated with a decreased level of consciousness or can manifest *only* during sleep [80].

Enhanced recognition of encephalitides in general has led to the development of diagnostic criteria specific for anti-NMDAR [82]: onset over less than three months of at least four “major” symptoms (e.g., abnormal behavior/cognition, a movement disorder especially in the context of a decreased level of consciousness, central hypoventilation, others); at least one of two laboratory features (abnormal EEG or CSF pleocytosis); and the exclusion of other diagnostic possibilities. In anti-NMDAR, EEG changes (focal or diffusely slow or disorganized activity, “delta brush,” a variant of delta rhythm in which the top of a slow and wide EEG waveform has the appearance of bristles of a brush) are common, even in the absence of seizure or frank epileptiform activity. CSF pleocytosis or oligoclonal bands (OGBs) are part of the criteria and are common findings.

Anti-NMDAR treatment considerations: Search for a teratoma is indicated in suspected anti-NMDAR. Anti-NMDAR is a treatable encephalitis. Roughly 80% improve with immunotherapy (first- or second-line agents) and/or oncologic treatment, although recovery may be slow [72].

Table 4. Pathophysiological Considerations in Antibody-Associated Syndromes; The Case of Anti-IgLON5 [71].	
Question	Answer, for Anti-IgLON5
Red flag for syndrome?	RBD, among others
Nature of antibody (Ab)?	Cell surface antigenic target; IgG4 >> IgG1
Does Ab appear in primary neurodegenerations?	No, compared to anti-NMDAR (IgM, IgA, or IgG) present in ~15% of dementias
Are there biomarkers or predictors of possible therapeutic response?	Yes, lower serum neurofilament light predicts response to long-term treatment
Receptor cross-linking at cell surface, with internalization?	Yes
Binding disruption at surface?	No, compared to interaction with “A Disintegrin and Metalloproteinase domain 22” (ADAM22) in anti-LGI1, with subsequent cellular internalization of ADAM22-anti-LGI1
Functional blockage of antigenic target?	No, compared to anti-GABA _B . Internalization of surface anti-IgLON5 with ensuing neurodegeneration
Irreversible internalization of antigen?	Yes
Evidence for complement activation or other inflammatory factors?	Yes, in animal models: increase in TGF-beta (tumor growth factor-beta), chemokines
Evidence for B- or T-cell activation?	Yes, increases in B-cell numbers in CSF
Evidence for other inflammation (microglial or astrocytic activation; cytokine mediation)?	Some evidence (lymphocyte infiltration, microglial activation)
HLA associations?	Yes, as discussed in text
Neuropathological correlations?	Hyperphosphorylated tau in neurons (hypothalamus, brainstem tegmentum) with neuronal loss—but not all studies concur

In an archival autopsy cohort, two untreated anti-NMDAR cases (one with comorbid small-cell lung carcinoma [SCLC]) and two additional cases (one with coexisting demyelination and another with a post-transplant lymphoproliferative disorder) were studied [87]. Of note, in the absence of immune treatment, the clinical triad of a movement disorder, abnormal behavior, and memory dysfunction correlated with plasma cell inflammation of basal ganglia, amygdala, hippocampus. The findings corroborate an antibody-mediated mechanism for the development of both dyskinesia and psychiatric/cognitive disturbance in anti-NMDAR.

Anti-CASPR2 (Contactin-Associated Protein-like 2), antigen at plasma membrane

CASPR2 is a transmembrane protein, one of two major voltage-gated potassium channel (VGKC)-associated antigenic targets. We discuss the second antigen, leucine-rich glioma inactivated 1 (LGI1), below. Discovery of anti-CASPR2, both as syndrome and autoantibody, advanced understanding of pathophysiology in neuromyotonia and Morvan's syndrome (the latter almost always in men, manifesting as the triad of encephalopathy, dysautonomia, and peripheral nerve hyperexcitability) [88-96]. We include a discussion of early historical reports, like Morvan's, in "**Supplementary Material**."

Compared to anti-LGI1, anti-CASPR2 is more likely to have a coexisting tumor (thymoma most commonly) as well as a spectrum of ongoing motor discharges, including neuromyotonia, myokymia, cramps, fasciculations, myoclonus in the legs on standing, or a low amplitude, very high frequency, and arrhythmic movement disorder described by Morvan as "fibrillary chorea."

Acquired neuromyotonia and Morvan's syndrome were recognized entities prior to the discovery of anti-CASPR2 antibodies. The clinical spectrum of anti-CASPR2 includes both, along with other phenotypes. Van Sonderen *et al.* [89] retrospectively analyzed a Spanish and Dutch cohort (n = 38) with serum or CSF positivity for anti-CASPR2. They identified seven "core" symptoms: cerebral symptoms, cerebellar symptoms, peripheral nerve hyperexcitability (including myotonia), dysautonomia, neuropathic pain, weight loss, and insomnia.

The last symptom is notable. A syndrome termed *agrypnia excitata* [90-92] (a "chase" for sleep, with motor overactivity—characterized by severe insomnia and "oneiric stupor" [hallucinations, motor agitation]), various dysautonomias (fever, perspiration, tachycardia, tachypnea, hypertension), and other motor activity including RWA—are all hallmark features of anti-CASPR2. *Agrypnia excitata*, however, occurs in other antibody syndromes such as anti-NMDAR (see above).

Considered a type of *status dissociatus* (a breakdown in EEG distinctions between wakefulness, sleep stages, and transitions to sleep or wakefulness), *agrypnia excitata*

polysomnographically is a "persistent state of subwakefulness . . . regardless of circadian rhythms" [21]. Liguori *et al.* [93] reported a case of a 79-year-old man with Morvan syndrome and VGKC antibodies whose polysomnography showed absent non-REM sleep architecture (sleep spindles, K-complexes, and delta waves were undetectable); atypically short REM epochs with RWA; and behavioral oscillation between calmness and agitation with dream enactment. Sleep architecture returned to near-normal after PLEX, and brain pathology showed only a microinfarct in the hippocampus without thalamic or brainstem changes.

Anti-CASPR2 treatment considerations: Anti-CASPR2 responds to treatment, including resection of thymoma if the tumor is detected [95]. Van Sonderen *et al.* [89] found that among patients without tumor, a majority showed full or partial response to immunotherapy. Shivaram *et al.* [96] reported eight patients who were treated with IV steroids and PLEX acutely, followed by pulsed IV steroids (a "long-acting" therapy, to use Grüter *et al.*'s [63] terminology). One patient died with refractory myasthenia with thymoma, but seven recovered "completely" after a mean follow-up period of ~20 months.

Anti-LGI1, antigen at plasma membrane

What are termed anti-VGKCs [97] in fact target LGI1 and CASPR2 specifically, as Irani *et al.* elucidated [88]. When we compare anti-LGI1 patients to those with anti-CASPR2, differences in their respective syndromes emerge.

Anti-LGI1, compared to anti-CASPR2, more commonly presents with amnesia, confusion, seizures, medial temporal lobe MRI findings, and, notably, hyponatremia (<135mM). As discussed above, anti-CASPR2 is associated with *status dissociatus* and *agrypnia excitata*, whereas anti-LGI1, albeit with various sleep disturbances [92,93], is more associated with RBD and PLMS.

Evidence for inflammation in anti-LGI1 CSF is often underwhelming [98].

Faciobrachial dystonic seizures (FBDS): We summarize five citations related to a distinctive movement disorder/seizure in anti-LGI1 [99-103].

FBDS are brief (lasting several seconds) and dystonic in appearance; they occur often in a state of reduced consciousness; a given paroxysm involves an arm and ipsilateral face in a stereotyped sequence. One hemibody is affected at a time, but the body side can alternate. Loss of awareness happens in the majority (66%); at onset, patients may experience "thermal" sensations, limb automatisms, and speech arrest. Epileptiform or slowed EEG waveforms appear in 24%. FBDS may manifest before the development of a full amnesic or confusional state or other evidence for encephalopathy or encephalitis. FBDS do not respond to

antiseizure medications, but they do to immune therapies in 50%, roughly within 30 days after initiation of treatment (most commonly IV steroids, although antiseizure medications were given concomitantly in a prospective trial [103]).

After 90 days of active FBDS, 56% develop cognitive impairment associated with both evidence of hippocampal structural and functional change as well as higher proportions of complement-fixing IgG1 and IgG4 antibodies. As we mention passing in **Table 4**, a combination of complement deposition and cellular internalization of ADAM22-IgG1-LGI1 (or ADAM22-IgG4-LGI1) complexes has been implicated in the pathogenesis of cognitive impairment, especially after delayed immune treatment for FBDS [99].

Anti-LGI1 treatment considerations: Anti-LGI1 responds to immunotherapy; there is a paucity of tumor associations. In Irani *et al.*'s series [88], anti-LGI1 had a significantly more robust response to immunotherapy (steroids, particularly) than anti-CASPR2. Early immune treatment may mitigate long-term cognitive sequelae.

Anti-Ma2, nuclear or cytoplasmic antigen

The Ma family of proteins is expressed in the brain and testes, both organs with a blood-tissue barrier. Cells expressing Ma have been studied in relationship to cancers, including melanoma and testicular germ cell tumors. Paraneoplastic Ma antigens (PNMAs; PNMA1 and PNMA2 in particular) are targets for two antibodies, anti-Ta (which recognizes PNMA2; anti-Ma2 is synonymous with anti-Ta [104]) and anti-Ma (which recognizes both PNMA1 and PNMA2). As Hoffman *et al.* [105] have described, young men with encephalitis and testicular germ cell tumors express anti-Ta/anti-Ma2, whereas patients of either sex—with a range of tumors—may express anti-Ma. We concentrate on the clinical picture associated with anti-Ma2.

Ten patients studied by Voltz *et al.* [106] had both anti-Ma2 and testicular cancer, with varied presentations. Five had seizures and six had memory loss (four had both seizures and memory loss). Hallucinations, abnormal eye movements (diplopia, oscillopsia), dysarthria, hypersomnolence, and ataxia were other features. Patient one presented with a syndrome of resting tremor, depression, and dystonia in addition to seizures and a memory disturbance. Patient ten manifested a mixed hypothalamic and parkinsonian syndrome with loss of libido, mutism, hypothyroidism, diabetes insipidus, and hypersomnolence.

In the early 2000's [107,108], 38 cases of anti-Ma2 were characterized in detail. The majority presented with a combination of limbic, brainstem, and/or diencephalic encephalitis. Notable aspects included eye movement abnormalities (vertical gaze paresis was most common; non-paretic eye closure in a parkinsonian presentation resembled an apraxia of eyelid opening) and diencephalic dysfunction

(13/38; features included excessive daytime sleepiness associated with low CSF hypocretin, cataplexy, hypnagogic hallucinations, unexplained weight gain, hyperthermia, and various endocrine disturbances related to hypothalamic-pituitary dysfunction).

In reviews of sleep disorders associated with neurological autoimmunity [80,109-111], anti-Ma2 has also been associated with excessive daytime sleepiness with cataplexy and low hypocretin/orexin, RWA, reduced sleep efficiency, increased sleep fragmentation, reduced sleep latency, absent sleep spindles, and absent slow wave sleep—the latter two aspects as seen in *agrypnia excitata*.

MRI (mainly T2/FLAIR) and CSF abnormalities are common in anti-Ma2 [108]. Multiple subcortical areas, from the thalamus superiorly to the medulla inferiorly, demonstrated lesions; medial temporal lobes structures were the most commonly involved cortical areas. The authors also reported on biopsy and autopsy material (they found T-cell inflammation commonly and multifocally), but we draw attention to a later study by Dauvilliers *et al.* [110] of a 63-year-old man with diencephalic encephalitis and anti-Ma antibodies (strong anti-PMNA2, weak anti-PMNA1 reactivity) with “almost exclusive inflammation and tissue injury in the hypothalamus.”

Anti-Ma2 treatment considerations: Over half of anti-Ma2 cases are associated with cancer, testicular tumors most commonly. In Dalmau *et al.*'s series of 38 patients [108], most received both oncologic (including orchiectomy) and immune therapy: 18 patients improved neurologically; 15 deteriorated. Younger men with testicular tumors are more likely to improve than those with non-testicular tumors [108,109].

In anti-Ma (with antibodies directed at *both* PNMA1 and PNMA2) Hoffmann *et al.* [105] reported that nine of 14 cases (eight female, six male) had histologically confirmed tumors—in lung, gastrointestinal tract, breast, and kidney, in addition to non-Hodgkin lymphoma and melanoma. In 13 of the 14, neurological disease progressed despite immunotherapy, although tumor disease stabilized with treatment in seven cases.

Anti-DPPX (Dipeptidyl-Peptidase-like-Protein 6), antigen at plasma membrane

In 2013, Boronat *et al.* [112] reported four patients with subacute encephalopathy with agitation, hallucinations, myoclonic jerks, and seizures. Three experienced a prodrome of severe, unexplained diarrhea and weight loss. Serum and CSF harbored antibodies directed against a 100 kD regulatory subunit (DPP6 or DDPX) of Kv4.2 (rapidly inactivating) VGKCs. DPPX is present on the cell surfaces of cultured hippocampal neurons as well as in the cytoplasm and on the membranes of myenteric plexus neurons. As with LGI1 and CASPR2 antibodies, DPPX antibodies are highly specific for the DPPX protein and not VGKC or adjacent proteins.

Oliver Tobin *et al.* [113], reporting on 20 anti-DPPX patients, noted a memory disorder in 16 of the 20 patients, various symptoms attributed to brainstem dysfunction (diplopia/blurred vision/oscillopsia in eight; dysphagia in six; myoclonus in eight), diffuse rigidity (in six), exaggerated startle/hyperreflexia (in six), and hyperreflexia (in six). Prodromal weight loss was common (in 12), but not solely related to diarrhea; five patients presented with anorexia. Thermoregulation, cardiac conduction, and bladder disturbances occurred in to patient #'s one, three, and seven, respectively. Seizures were uncommon (two patients). Tumor screening discovered B-cell neoplasms in two of the 20.

Sleep manifestations were frequent. Nine reported sleep "disruption" (six with insomnia); PLMS occurred in five. One patient studied polysomnographically evinced *simultaneous* REM (sawtooth EEG waves) and non-REM sleep (sleep spindles, K complexes)—a mixed picture consistent with *status dissociatus*. A subsequent 2023 review [114], with focus on sleep disorders in anti-DPPX in the Mayo Clinic experience, draws attention to RWA, RBD, obstructive sleep apnea, as well as the case of *status dissociatus* just mentioned; complete polysomnography was available for only three in their small sample (n = 6).

Hara *et al.* [115], reporting on 39 patients from 2013-2017 (nine newly reported in their paper), found that 67% overall presented with a triad of weight loss/diarrhea, cognitive/memory dysfunction, and CNS "hyperexcitability" (exaggerated startle, myoclonus, tremor, or seizures).

Anti-DPPX treatment considerations: Anti-DPPX responds to immunotherapy, as is true for other surface-directed antibody syndromes. In Hara *et al.*'s [115] review, overall improvement was seen in 60% (for their new nine cases, modified Rankin scores were no greater than two—suggesting modest impairment—in seven cases, after 12-36 months of follow up).

Anti-GABA_BR (Gamma-aminobutyric Acid "B" Receptor, B1 subunit), antigen at plasma membrane

A previously healthy 55-year-old woman [116] developed diplopia and fluctuating bilateral ptosis, then, two years later, dysphagia and tongue weakness. Three years after presentation, polysomnography revealed a reduction in REM sleep. Seven years after the presentation, she experienced episodes lasting a few hours characterized by early, heavy sweating, nocturnal respiratory crises, then respiratory failure. At one point during these bouts, she experienced 24-48 hours of fasciculations, cramps, and hyperreflexia. EMG found no evidence for ongoing motor activity. Whole-body MRI found no tumor, and her brain MRI was normal, as was her CSF. Various polysomnographic studies found evidence of *agrypnia excitata* with finalistic movements of the type described in our discussion of anti-IgLON5. During her protracted illness, improvement in sleep architecture and other aspects of her

episodes was credited to various immune-modulating trials.

In anti-GABA_BR, sleep + movement disorders have been poorly characterized if reported (except the description provided above by one group [116,117]). Zhu *et al.* [118] conducted a retrospective analysis of 14 Chinese patients with anti-GABA_BR: abnormal sleep patterns occurred for six; "[four] patients slept more, whereas two were restless and did not sleep at night." No polysomnography was reported. Similarly, Guan *et al.* [119] retrospectively studied 18 Chinese patients: three had a "sleep disorder," with no further description of specifics.

Lancaster *et al.* [120] published a series of 15 patients, all of whom had seizures as part of their encephalitic syndrome. Cancer was common: 7/15 had an identified tumor, most commonly SCLC. One patient presented with "abnormal sleeping habits," but details were not reported.

Höftberger *et al.* [121] reported 20 patients with anti-GABA_BR: the general presentation of seizures, memory loss, confusion, and the presence of SCLC echoes Lancaster *et al.* But they also observed ataxia, opsoclonus/myoclonus, and *the presence of additional antibodies*: among those with SCLC, anti-SOX (Sex-determining region Y-related HMG-Box [high mobility group Box]), anti-amphiphysin, and anti-Ri (or anti-ANNA2, antineuronal nuclear antibody type 2)—SOX, amphiphysin, and Ri/ANNA2 are all nuclear or cytoplasmic antigens. Among those without SCLC, anti-glutamic acid decarboxylase (GAD) and anti-NMDAR (NR1 subunit) were observed in addition to anti-GABA_BR. No sleep abnormalities were reported.

The association with other antibodies is notable. In Lancaster *et al.*'s series [120], 3/15 had both anti-GABA_BR and anti-GAD. Bonorat *et al.* [122] found, in association with SCLC and anti-GABA_BR (n = 8), that one patient co-expressed anti-Hu (anti-ANNA1) and two anti-GAD. In a single case of "clearly . . . 'classical'" anti-IgLON5, with a gait disorder and severe parasomnias, anti-GABA_BR was present in addition to anti-IgLON5 [123].

Anti-GABA_BR treatment considerations: Anti-GABA_BR responds to immunotherapy and concurrent treatment of tumor (*viz.*, SCLC). In a systematic review, McKay *et al.* [124] reported an 86% improvement rate with immunotherapy and relevant oncologic therapy in anti-GABA_BR.

Mimicry in Antibody-Associated Disease

Identification of an antibody may result in phenotype "creep"—the thought or presumption that a syndrome's spectrum should broaden *because* of an unexpected antibody titer [125]. In the case of mimicry, an analogous problem arises: if, for example, one clinically suspects anti-NMDAR or anti-LGI1 (e.g., with oral dyskinesias), then what significance accrues to an unexpected antibody titer? We discuss three examples of antibody syndromes that mimic others.

Anti-Neurexin-3-alpha, antigen at plasma membrane

In five cases reported by Gresa-Arribas *et al.* [126], four were women; the clinical picture was consistent. A young person (<50 years) experiences a rapid decline in level of consciousness with seizures, subtle orofacial dyskinesias, and central hypoventilation. Two of the five died and the other three only partially recovered despite treatment. All three displayed ongoing cognitive deficits, though follow-up was variable (2-36 months). All patients received high-dose corticosteroids with one additionally receiving IVlg and another cyclophosphamide. Sustained remission was observed in a single case report of a 59-year-old woman with new-onset seizures, hallucinations, and aphasia who was found to have anti-neurexin-3-alpha antibodies in CSF. She was initially treated with high-dose corticosteroids and plasmapheresis, followed by a 1-year course of rituximab [127]. This patient had no residual cognitive deficits at 3 and 6 months. The presentation calls to mind either anti-NMDAR and anti-IgLON5 (orofacial dyskinesia and central hypoventilation occur in both), but Gresa-Arribas *et al.* found expression of anti-Neurexin-3-alpha in all cases. Neurexins are polymorphic neuronal surface proteins that are involved in synapse formation and maturation.

Anti-ZSCAN1 (Zinc finger- and Scan domain-containing protein 1), nuclear or cytoplasmic antigen

Based on a proteome-wide screen, a rare pediatric syndrome of rapidly developing obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysfunction (ROHHAD) has been associated with expression of anti-ZSCAN (in 7/9 ROHHAD cases) and with neuroblastic tumors (in 8/9) [128]. ZSCAN is expressed particularly in hypothalamus—reminiscent of anti-Ma2, in which hypothalamic-pituitary dysfunction is a hallmark.

“Basal ganglia antibodies” and Anti-D2R (DA-2 Receptor), receptor at plasma membrane

In 2001, Dale *et al.* reported a dyskinetic form of basal ganglionic encephalitis resembling von Economo's encephalitis lethargica in 10 children with prior streptococcal infection [129]. In 2009, they gathered CSF and serum in 20 cases, not all of whom had known streptococcal infection, to discover that the dyskinetic phenotype of encephalitis (with sleep disorder and psychosis) tested positively for anti-NMDAR in 10 [130]. In 2012, 17 children, again with basal ganglionic encephalitis, were compared to groups with Sydenham chorea, Tourette syndrome, and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) [131]. Twelve of the 17 tested positive for anti-D2R, but also 10/30 with Sydenham and 4/44 with Tourette, but 0/22 with PANDAS.

Even in the early 2001 report, the research group suspected autoimmunity directed against “basal ganglia,” and an antibody specific to the DA-2 receptor corroborates that

view, but the papers as a group speak to the possibility that syndromes (anti-NMDAR and anti-D2R) can mimic each other. Indeed, in a study of 48 pediatric cases of first-break psychosis, eight elaborated antibodies—three with anti-D2R, five with anti-NMDAR, and one with *both* anti-D2R and anti-NMDAR [132]. Likewise, in a pediatric sample studying chorea and encephalopathy following HSVE, either anti-NMDAR, or anti-D2R, or both anti-NMDAR and anti-D2R has been reported [133].

Restlessness in a State of Repose: Willis-Ekbom Syndrome

In the 17th century, Thomas Willis described an affliction of motor restlessness when persons “betake themselves to sleep”; Ekbom reported a syndrome of discontinuous paresthesiae associated with a need to move. For a discussion of historical descriptions of Willis-Ekbom syndrome, please see “**Supplementary Material**.”

Based on a 2014 consensus statement [134], criteria for Restless Legs Syndrome (RLS) include features not significantly different from Willis's and Ekbom's descriptions of akathisia as well as features “not essential” for diagnosis, despite their *very close* association with RLS, including: 1. PLMS; 2. PLMW; 3. DA treatment response, although we add that treatment options are myriad [135]; 4. a family history of RLS among first degree relatives; and 5. a lack of “profound” daytime sleepiness. Högl and Stefani [43] elaborate on those aspects, then broaden our view of RLS as a movement-disorder comorbidity.

RLS and PLMS, the latter diagnosis based on EMG criteria mentioned earlier, commonly occur together, although either PLMS or PLMW can occur without RLS. PLMS in isolation could be a biomarker of genetic susceptibility to RLS; linkages based on genome-wide association studies are summarized in a recent and exhaustive review of RLS by Manconi *et al.* [136]. Furthermore, both RLS and PLMS frequently manifest in other movement disorders—here we summarize Högl and Stefani's long list: various Parkinsonisms (PD, MSA, DLB), tauopathies (PSP and corticobasal syndrome), essential tremor, Tourette syndrome (associated with maternal, not paternal RLS), various dystonias (cervical dystonia, blepharospasm, some generalized dystonias), Friedreich and other ataxias (especially spinocerebellar ataxia types 2 and 3 [SCA2 and SCA3]), propriospinal myoclonus of sleep onset, and excessive fragmentary myoclonus of sleep (“ubiquitously” comorbid with RLS).

A DA paradox?

Ferré *et al.* [9] describe a seeming DA paradox in RLS. Acute DA receptor antagonism commonly results in akathisia during wakefulness (an untoward neuroleptic side effect, which can also develop in tardive fashion). On the other hand, RLS, an akathisia, is a nocturnal phenomenon or at least one in recumbency, as is PLMS (for clarity, periodic leg movements of sleep), and both conditions respond to dopaminergic treatment. But prolonged use of DA agonists or high doses of

those medications can result in “augmentation,” a worsening of RLS during treatment. Studies over time have built an argument for increased DA synthesis in untreated RLS [137].

The DA “paradox” has treatment implications. Higher doses of DA agonists can augment RLS severity but attempts to decrease or to discontinue the agonist are not tolerated, precisely because the restlessness persists or worsens. In such situations, transitions to other classes of drug (e.g., opiates) may be necessary, but it is often the case that combination treatment is necessary (e.g., a lower dose of agonist plus an opiate) [138].

DA tone in context; genetics and iron in RLS

Traditionally, DA has been implicated in the modulation of cortically driven movement, and DA’s role in motivation and learning, both in terms of a midbrain DA neuron’s tonic or phasic firing (phasic in very short time frames, over seconds) has been investigated in detail [139]. While there are suggestions that hypothalamic and striatal DA vary over the course of a day, the mean rate of midbrain DA neuronal firing may not [140,141]—the last point has been debated [142]. Nevertheless, DA “activity” in different parts of the brain, particularly the corpus striatum, to which midbrain DA neurons project, may vary over 24 hours as a function of multiple factors—e.g., the activity of DA transporters [141], modulation of DA action by glutamate and acetylcholine, or control mediated by DA and adenosine receptors especially in ventral corpus striatum [9].

Allen [143] has authoritatively discussed the related roles of genetics and of brain iron stores in RLS. Among several risk alleles (see also 136), BTBD9 on chromosome 6p is associated with RLS, PLMS independently of RLS, and decreased peripheral iron, as occurs in iron-deficiency anemia. Treatment of peripheral iron deficiency with decreased serum ferritin is well known to be effective in RLS, and RLS prevalence is roughly nine times greater in iron-deficiency anemia than in the general population.

A threshold of critical post-synaptic DA signaling exists, Allen has maintained; below it, RLS symptoms manifest. In patients who respond well to dopaminergic treatment, DA “activity” varies during the day without dipping below that threshold, with less at night and more during waking hours. In augmentation, ongoing treatment with dopaminergic agents results in larger swings in DA activity (more DA “activity” during the day with a nadir at nighttime), with more time spent below threshold and greater RLS symptomatology as a consequence. Low dosing and longer drug half-lives mitigate the problem.

Spinal excitability

Before 2020, reports had surfaced that a small diencephalic cluster of DA neurons—called A11 located in hypothalamus, dorsal to mesencephalic “A” groups [144]—projects densely to all Rexed laminae of spinal cord, especially to the sensory dorsal horn and intermediolateral grey matter [145-148].

Evolutionarily conserved, A11 contributes to modulation of spinal motor networks, perhaps by inhibition of sensory afferents [145]. A11 projections descend through periaqueductal grey to terminate more densely in lumbar than in higher levels of spinal cord [146], and A11 lesioned rats are hyperactive with long-lasting reduction in sensory thresholds [147].

Spinal cord disruption, in a decerebrate animal with transection at the level of the midbrain colliculi or in humans with cord injury, results in periodic leg movements that resemble both the triple flexion response (flexion at the ankle, knee, and hip) or various combinations of movements in PLMS or PLMW (for clarity: PLMW = periodic leg movements or resting wakefulness; both PLMS and PLMW exhibit extension of the big toe, partial flexion at the ankle, knee, and hip) in response to mechanosensitive and/or nociceptive afferents; disinhibition of flexor reflexes also occurs in the context of intact supraspinal influence, specifically in rest and sleep [148].

Ferré *et al.* [149] note that triple flexion, PLMS, and PLMW may all involve the same spinal “generator.” Hypoactive adenosinergic inhibition of that generator, if indeed causal, introduces novel therapeutic options, including use of adenosine agents such as dipyrindamole in the treatment of the movement disorder.

Whether DA in spinal cord influences co-contraction of flexors and extensors is best addressed in a discussion of dystonias with diurnal variation.

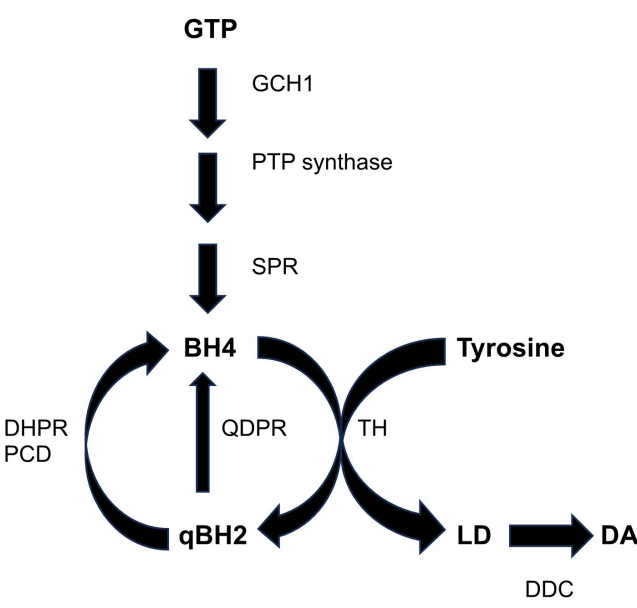
Time-of-Day Variation in Dystonia

Segawa *et al.*’s original 1976 report [150] of “marked diurnal fluctuation in dystonia” remains a compelling description of a phenotype: typical onset in childhood, no birth or developmental abnormality, insidious onset of dystonia or other dyskinesia, progression typically over five years, a pattern of bodily involvement (if a leg is first involved, then the ipsilateral arm becomes dystonic, then the contralateral leg, then contralateral arm), marked diurnal variation (worse in the morning), and compelling response to low doses of levodopa. Recent reviews discuss many variant presentations, “look alikes,” and “dystonia plus” syndromes [151,152]. We undertook a review to summarize the many dystonias associated with single gene mutations that characteristically vary with the time of day. We describe our literature search method in “**Supplementary Material**” to this paper. **Table 5** summarizes our findings.

Relevance of tetrahydrobiopterin (BH4) and DA pathways (Figure 2)

We schematize the synthesis, salvage, and recycling of BH4, an essential cofactor for the rate-limiting enzyme TH; in **Figure 2**. We also address the relevance of other gene associations, as cited in **Table 5**.

Table 5. Reports (2017-2023) of Dystonias with Diurnal Variation.	
First author, reference number	Key Findings
Stephen [10,153], DePablo-Fernandez [154]	DYT/PARK-GCH1: DRD, autosomal dominant (AD), rarely autosomal recessive (AR), dopa responsive, with diurnal variation (worse in evenings), sleep benefit, associated with spasticity and familial cerebral palsy; normal dopamine transporter (DAT) studies; Atypical features include parkinsonism in adult presentations, myoclonus, and various psychiatric comorbidities, including obsessive-compulsive disorder Marked diurnal variation characterizes DRD. An early sign is a distal dystonic posture in the leg, a pes equinovarus in a young person, more commonly among females. DYT/PARK-TH: DRD, AR, dopa responsive, with diurnal variation, associated with myoclonus, spasticity, oculogyric crises; deep brain stimulation (DBS) of benefit. DYT/PARK-SPR: DRD, AR, rarely AD, dopa responsive, developmental delay, high CSF biopterin/dihydrobiopterin. Additional rare AR form involves gene encoding PTP synthase. MxMD-ADCY5: “mixed” refers to its clinical pleiotropy: dystonia, chorea, myoclonus, tremor, triggered by transitions in sleep. DYT-DDC: AR, diurnal variation, sleep disorder, sleep benefit, chorea, developmental delay, truncal hypotonia, oculogyric crises, ptosis, autonomic symptoms
Keller Sarimento [155], Wong [156]	New genes responsible for DRD DnaJC12: bi-allelic loss-of-function mutations cause developmental delay, hyperphenylalaninemia, with favorable response to BH4 and levodopa SLC18A2: infantile onset DYT/PARK; dopamine agonists effective, but not levodopa Wong describes other defects in BH4 metabolism (DHPR, PCD); also describes posterior leukomalacia in DYT/PARK-GCH1
Carecchio [157]	PDE10A related disorders: both AD and AR; carriers of dominant mutations with homogenous phenotype: early onset (<15 years old), <i>chorea</i>, normal cognition; diurnal fluctuations in childhood with progressive spread of chorea during life.
Pérez-Dueñas [158]	Periodic dystonic attacks, often associated with orolingual dyskinesia, with diurnal variation (with sleep benefit) in SLC6A3. ATP1A3: paroxysmal paralysis, dystonia, ataxia, and dysphagia; fatigue a trigger. Glut1 deficiency: fatigue-associated acute ataxia, quadriplegia, dystonia.
Weissbach [159-161]	Movement Disorders Society Gene Review: pathogenic variants in five genes associated with DRD: aside from those mentioned above, QDPR Most common DYT/PARK-GCH1 variant is a single nucleotide variant leading to a premature stop codon in exon 1 Discussion of genetic (monogenic) atypical PD and DRD. Red flags for atypical PD: supranuclear gaze palsy in ATP13A2 and hypoventilation in mutations of the DCTN1 gene (Perry syndrome: described in a Canadian family, AD, adult-onset parkinsonism, sleep problems and respiratory trouble; may have PSP phenotype)
Li [162]	Case report in “DYT24”-ANO3, a “Chinese dystonia”: 12-year-old female with left leg abnormal postures since age 11 which improved with sleep; then a progressive gait disturbance with eventual response to DBS.
Abbreviations used: ADCY5: Adenylate Cyclase 5; ANO3: Anoctamin 3; ATP1A3: Adenosine Triphosphate Synthase, Sodium/Potassium Transporting, Alpha-3 Polypeptide; ATP13A2: Adenosine Triphosphate Synthase, Sodium/Potassium Transporting, Alpha-2 Polypeptide; BH4: Tetrahydrobiopterin; DCTN1: Dynactin; DDC: Dopa Decarboxylase; DHPR: Dihydropteridine Reductase; DnaJC12: DnaJ Heat Shock Protein Family Member C12; DRD: Dopa-Responsive Dystonia, Segawa Disease; DYT/PARK: Dystonia/Parkinsonism; GCH1: Guanosine Triphosphate (GTP) Cyclohydrolase 1; Glut1: Glucose Transporter 1; MxMD: Mixed Movement Disorder; PCD: Pterin-4a-Carbinolamine Dehydrase; PDE: Phosphodiesterase; PTP: 6-Pyruvoyl-Tetrahydropterin; QDPR: Quinoid Dihydropteridine Reductase; SLC6A3: Solute Carrier Family 6 Member A3 (encodes the dopamine transporter or DAT); SLC18A2: Solute Carrier Family 18 Member A2 (encodes vesicular monoamine transporter 2 or VMAT2); SPR: Sepiapterin Reductase; TH: Tyrosine Hydroxylase	



Presynaptic (DA neuron)	Postsynaptic medium spiny neuron, corpus striatum (e.g.)	Pre- and Postsynaptic
SLC18A2 (VMAT2), SLC6A3 (DAT), DnaJc12, ?ATP13A2 (cellular uptake of polyamines)	ADCY5, PDE10	ATP1A3 (sodium/potassium pump), Glut 1, ?DCTN1 (axonal integrity), ?ANO3 (sodium/potassium channel trafficking in dorsal root ganglion)

Abbreviations are those used in Table 5 or in the text, except: LD = levodopa and qBH2 = quinonoid dihydrobiopterin.

DnaJC12 interacts with TH in mesencephalic DA neurons (biallelic loss of function in DnaJC12 is associated with hyperphenylalaninemia); SLC18A2 encodes for VMAT2, which stores DA in vesicles before release into the synaptic space (155). The enzyme encoded by PDE10 is highly and selectively expressed in medium spiny neurons of the corpus striatum; it is involved in the degradation of both cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Alterations in ADCY5, the gene that encodes an adenyl cyclase (involved in DA receptor activity postsynaptically) may result in a gain of function associated with increased intracellular cAMP (157).

Figure 2. Relevance of BH4 and DA pathways; other relevant gene associations.

Why co-contraction in dystonia?

Pleiotropy is the rule rather than the exception in all the syndromes described in **Table 5**, but we concentrate on the phenomenon of co-contraction of agonist and antagonist muscles that results in a fixed posture in dystonia.

Muscles across joints achieve points of equilibrium in external space, based on coordinated activities of agonist and antagonist muscles in a limb. DA as well as other amines may directly influence neural modules in cord, as we discussed with specific reference to the A11 DA cell cluster.

Broadly tuned cortical neurons probably do not stipulate the specific brainstem or spinal cord modules to generate a combination of muscle forces—what has been termed a “motor field”—with nested equilibrium points [163]. To

address the surfeit of potential effectors in a normal action, a motor task is more likely divided into well-timed subtasks associated with discrete neural substrates. Both subcortical (in the broadest sense of “subcortex,” even those in cord) and cortical modules may parse a large computational problem into parts [164].

Co-contraction of muscles that should not co-contract is a timing problem in miniature: agonists and antagonists should not contract simultaneously at any given moment, and co-contraction is powerfully inhibited by DA [165]. As many clinical presentations in DRD suggest, co-contraction can also vary across the time frame of a day. DA dysregulation is not an epiphenomenon of a clock disturbance: the dysregulation itself may result in mis-timing across momentary, short, and long intervals.

Conclusions Relevant to the Time Domain

Table 6 offers our major points and shortcomings in this paper.

Timing is a function of central and peripheral clocks whose interaction happens across a wide net; many lesion locales, including in dopaminergic nuclei, could disturb the percept of time. Albrecht [166] has quipped that, at least for mammals, there may be as many biological clocks as there are cells in the body.

Variable presentations in antibody-mediated syndromes and pleiotropy in genetic disease may set the stage for diagnostic uncertainty, but suggestions of a timing disturbance are hints, readily elicited by history or examination, that can aid in clinical accuracy.

Motor variation during a waking day happens both in PD and among normals. But, in PD, there is less of a difference between the most and least active epochs during the day. In RBD, absence of atonia predicts clinical Parkinsonism once alternative explanations have been excluded.

Is clock dysfunction evidence of a degenerative process?

It need not be, insofar as anti-IgLON5, anti-Ma2, anti-DPPX, and anti-LGI1 (just four examples) are not neurodegenerative in the same way as PD. But RBD is a red flag in those antibody syndromes as well as in Parkinsonism both before and after the advent of motor or cognitive signs or both.

Hyperkinesia in a state of reduced consciousness is

not pathognomonic of any disease, but observing the hyperkinesia invites consideration of context, especially autoimmunity. By history or laboratory study, evidence of *status dissociatus/agrypnia excitata* should prompt suspicion of anti-NMDAR, anti-CASPR2, and anti-DPPX. Also, as **Table 4** suggests, inflammatory disease and neurodegeneration are not mutually exclusive: immune mediation may contribute to neural dysfunction or frank cell loss in concert with a primary pathogenic process or in the absence of such a process.

The major implication of a temporal disturbance is that a lesion may result in a system disturbance, but the disturbance itself, not necessarily lesion localization, is the interest. Frank absence of a lesion, likewise, does not obviate a network problem, especially if key pathogenic variables are genetic and metabolic in nature, as in **Table 5**.

With respect to the hypothalamic A11 DA group, Earley *et al.* [167] compared six RLS and six age-matched control autopsy cases to find that there was no significant difference in A11 cells between groups. The authors conceded that A11 could still be involved in RLS pathogenesis; their caution is appropriate in light of evidence that DA deficiency can occur in the absence of DA neuronal loss, as has been described in DRD [168].

Similarly, in dystonias generally, neuropathological reports have been limited in their number and scope—e.g., a single report of nigral cell loss in a variant DRD [169]. A general caution still applies: absence or presence of a lesion neither obviates nor confirms a network dysfunction that can be ascertained clinically.

Table 6. Main findings and shortcomings of our review.	
1.	Movement disorders may vary with time of day and with mental state, including states of reduced consciousness.
2.	Despite hypothalamic control of biological timing, many cell populations, including dopaminergic nuclei, have “clock” functions.
3.	Parkinsonism and the synucleinopathies illustrate our argument, in light of several aspects: a behavioral disorder in sleep before the appearance of motor signs, diurnal variation in severity of motor manifestations, and nocturnal movements.
4.	A role for an inflammatory or autoimmune mechanism for timing or state variability in movement disorders becomes especially clear in various antibody-associated diseases.
5.	Major entities to consider relevant to point four include: anti-IgLON5, anti-NMDAR, anti-CASPR2, anti-LGI1, anti-Ma2, anti-DPPX, and anti-GABA _B R.
6.	Willis-Ekbom (restless legs syndrome) is an akathisia that implicates both iron and dopamine; clinically, it is a movement disorder associated with either recumbency or sleep (especially given the relationship between Willis Ekbom and stereotyped periodic leg movements of sleep or resting wakefulness).
7.	Dystonias specifically with diurnal variation are often monogenic, and we discuss them in relationship to the pathways of dopamine synthesis.
Shortcomings	
1.	Our methods for literature review were various, not consistent.
2.	Ours cannot be considered a systematic review, but rather simply a “primer.”
3.	We merely speculate on possible dopamine-related mechanisms of dystonia.
4.	We do not provide a neurological localization for timing disturbances and associated movement disorders.

What is the relationship between putative cause and specific phenotype?

To say, “one genetic abnormality, multiple phenotypes,” as one might ascertain from **Table 5**, under-represents how multiple mutations can happen in a gene. To say, “multiple phenotypes, one disease,” as could be said of antibody-mediated syndromes, probably reveals how little we understand about whether (or if) production of an antibody *causes* a network disturbance—and if it does, the mechanism by which a time-of-day manifestations occur is not therefore obvious.

In many neurodegenerations, observed pathology may or may not relate to a specific network disturbance in the time domain. Alpha-synuclein aggregates in various non-brain, peripheral locales, including salivary glands, colon, and skin [170]. In AD, with its stereotyped and staged progression in the brain neuropathologically, RBD is rare at all stages of the disease. Likewise, RBD is not a phenotype in HD. Nevertheless, RLS and PLMS are present in synucleinopathy, tauopathy, and some trinucleotide-repeat diseases. Many lesion locales can result in network derangement [171], perhaps across the breadth of the neuraxis, so that specific localizations are not possible.

The relationship between etiology and phenotype begs a question that arises about pleiotropy in genetics [172]: if pleiotropy refers to “different kinds of one-to-many maps,” then *what map is in question?* Clinical phenomenology in the time domain or in relationship to mental state is an underexplored landscape in the study of movement disorders.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Acquisition, analysis, interpretation of data; drafting of work, revision for content; approval of publication; accountability for all aspects of the work: J. A. S., S.C., M.C., E.M.

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Data Availability Statement

All relevant data are contained within the article. The original contributions presented in the study are included in

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