Parkinson's Dopaminergic Synaptopathy: Why the Delay in Motoric Symptoms?

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Abstract

Among the neurodegenerative diseases, Parkinson's Disease (PD) is second only to Alzheimer's dementia in prevalence, and is expected to increase three fold over the next 50 years with population median, age related increases. Although its etiological basis is increasingly well understood, key areas remain to be elucidated, particularly in how its motoric symptoms are related to the underlying cellular events that ultimately give rise to the observed oscillatory and behavioral changes. The onset of a progressive neural degeneration commences years before motoric symptoms make their outward appearance, which are only seen after substantial depletion of dopamine reservoirs and extensive crippling of the synaptic neurotransmission machinery. Such prolonged functioning implicates a resilient mechanism that is traced to non-linear, oscillatory performance, whose structure may be described by current models of sparsely connected synchronization.

Keywords: Parkinson's; Alpha Synuclein; Beta Oscillation; Dopaminergic; Sparse Synchronization; Synaptopathy

Introduction

Among the neurodegenerative diseases, Parkinson's Disease is second only to Alzheimer's dementia in prevalence, and is expected to increase three fold over the next 50 years as the mean population age continues to rise. Demographically, nearly one in seven individuals above 60 exhibit some combination of disease symptoms, with an increase in prevalence of about 15% per decade thereafter. Generally, it is more common among individuals of European descent than among Asians or Africans, and slightly more prevalent among men than women [1].

PD is designated a movement disorder, of which the cardinal symptoms are tremor, bradykinesia, rigidity, and postural abnormalities. Although its etiological basis is increasingly well understood, key areas remain to be elucidated, particularly in how its symptoms are related to underlying cellular events that ultimately give rise to the neurophysiological and motoric pathologies. A number of studies now indicate that PD's motor abnormalities entail aberrations in neural oscillations throughout the chief motor nuclei, the striatum, globus pallidus, substantia nigra (SN), subthalamic nucleus (STN), and thalamus. These are precipitated by dopaminergic neuron loss originating in the synapses of SN projection neurons where they innervate the striatum [2,3]. The resulting operational losses consecutively impact neighboring nuclei through their associated connectivity; subthalamic nucleus oscillations and phase amplitude coupling, for example, are more extensively affected in the correspondingly affected hemisphere in PD patients [4].

Oscillations are ubiquitous in the brain where they are postulated to serve the crucial role of information transfer within and across spatial domains, and to link globally pertinent to regionally executed events [5]. Their significance was first made apparent when they were seen to address a conundrum of the former chief model for cognitive information processing, Wiesel and Hubel's abstractive proposal [6]. In this earlier scheme central nervous system neurons were hypothesized to progressively assimilate more abstract characteristics from lower level neurons that retained simpler information content. However, the hypothesis of receding abstraction was complicated by the progressive restriction in numbers of complex neurons at higher scales. Oscillations, by contrast, were capable of association in virtually any combination, continually disengaging and reforming new combinatorial variants [7,8]. Hence, there was no information regress and no corresponding and progressive shrinkage of the neuron pool.

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Oscillation changes during PD are complex, occurring within and between the chief movement nuclei, and displaying frequency as well as power shifts, cross frequency coupling, and anti-parallel changes [1,9,10]. Preceding these multifaceted changes, there is an extended prodromal phase marked by a progressive and selective loss of dopamine transmission. Beginning in the synaptic terminals, dopaminergic neurons of the substantia nigra undergo degeneration, that is then followed by the loss of axons and soma and, eventually, the entire nigrostriatal pathway. Only after decades of degeneration, and in a substantially dopamine depleted state, are the oscillatory changes and motoric symptoms observed [3]. Why the impact of this initial cellular phase is so delayed and how it may ultimately contribute to its physiological pathology will be the focus of this review.

Prodromal, Dopaminergic Synaptopathy

Dopaminergic degeneration

The progressive neural deterioration of PD commences years before the outward appearance of its motoric symptoms, setting into motion processes that by the time of their detection are difficult to resolve. During this long latent phase PD's cellular triggers subtly and progressively disfigure key operational machinery in the presynaptic zone of the substantia nigra, dopamine bearing neurons [3]. Its principal cellular indicators are prominent, proteinaceous inclusions, termed Lewy Bodies, which are formed from aggregates of a misfolded protein essential for synaptic vesicle docking at the active zone, alpha-synuclein. Excessive accumulation of Lewy Bodies has been shown to precede synaptic loss. Additionally, numerous secondary effects impact the synapse's supramolecular architecture, not only within the motor nuclei, but also in the prefrontal and cingulate cortex tissues [11,12]. More than twenty proteins needed for synaptic transmission and dopamine processing are affected; hence, PD has been additionally classified as a synaptopathy. These losses together are cited as the basis for patient experience during this phase of multiple non-motor symptoms, including depression, obesity, hyposmia, sleep abnormalities, and constipation.

Most cases of PD are sporadic and of unknown cause, and so the determination of a single precipitating factor is still not fully resolved. However, familial predispositions have established the strongest genetic link to mutations of the gene SNCA, which encodes the presynaptic protein alpha synuclein [13,14]. Alpha synuclein is the main component of Lewi Bodies and, together with its known key role in synaptic vesicle docking, mounting evidence of its influence on dopaminergic metabolism indicates a chief role in the events that ultimately yield the aberrant oscillatory patterns seen in basal ganglia and neighboring nuclei in later stages of Parkinson's.

Effects on dopamine metabolism are exerted at two levels, in the synthesis of dopamine and in its re-uptake and compartmentalization into synaptic vesicles in preparation for release. For example, increases in alpha-synuclein concentration have been shown to negatively regulate tyrosine hydroxylase conversion of L-tyrosine to L-DOPA and that of L aromatic amino acid decarboxylase conversion of L-DOPA to dopamine [15,16]. Similarly, both reuptake and compartmentalization steps are also negatively affected. Thus, there is a profound effect of the protein on the level of dopamine available for synaptic transmission [17].

Transmission failure is further amplified at the level of the vesicular machinery, where normal alpha synuclein functions together with a protein designated CSP to chaperone synaptic vesicles to the synaptic active zone, at which tethering, docking, and membrane fusion occur. In PD patients however, missense mutations shift the normal equilibrium between soluble monomer and bound oligomer to one increasingly favoring the bound state [3], impeding the steps immediately prior to release. Failure of proteosomes to degrade the ensuing complexes is apparently the cause of a proliferating increase in concentration that leads to synaptopathy. Interestingly, in a study of mice models overexpressing human alpha-synuclein, the total number of synaptic vesicles was not altered, whereas their spatial distribution was oriented away from the active zone; that is, a preponderance of vesicles were not undergoing movement to the point of vesicular release [18], consistent with alpha synuclein role in vesicular movement.

Despite the progressive and significant synaptopathy of the substantia nigra, nonetheless, PD patients fail to display symptomatic motor deficits until after significant degeneration has occurred. Since motor symptoms are closely related to oscillatory activity, how dopaminergic synaptopathy may impact oscillations and why the process is so extended remain unsettled questions. This is also to say that between the relatively abundant experimental findings on dopaminergic neuron degeneration and a less, but reasonably well studied domain about neural oscillators there is a poorly understood area needing elucidation to explain the persistence of function in the brain's motor regions of PD patients.

Oscillatory changes in PD

Plausibly, inferences about this unknown zone extrapolate from what is known of oscillator operation, whose features of operation are increasingly well understood both within and without the brain's motor nuclei. The intrinsic ability of oscillators to combine, for example, is known to be achieved by the synchronization of their frequencies, that is, they mutually adapt their rhythms, a physical observation made centuries ago by Huygens [19]. Because oscillations are ubiquitous throughout the nervous system they are capable of interareal as well as interlevel combination. Neural synchronization in the gamma frequency range, notably, has been reported in cortical and subcortical structures [2]; their ubiquity throughout the nervous system, accordingly, has been hypothesized to explain how cortical structures communicate with the basal ganglia. Although the mechanisms by which neural synchronization occurs are not precisely known, spike timing appears to be an important factor, though a complex one [20]. Oscillations enhance and lessen neuronal spike probability by increasing and decreasing the axonal sensitivities to incoming trains of stimuli, typically through localized voltage effects. Intrinsically, therefore, synchronous modes are preferred; that is, through phase alignment their frequencies can resonate in unison. Termed phase locking, resonating in unison has the important effect of enhancing information transfer [19,21], hence of facilitating communication between brain domains.

In the brain, however, rigid or full phase locking is rarely, if ever, achieved, a feature described by the Theory of Weakly Coupling Oscillators [19]. Some insight into why oscillators resonate in less than perfect synchrony can be inferred from the role they play in behavior. Since oscillators need to generate a multiplicity of functionally salient outcomes there is a basic need to reform multiple and changing combinatorial units. This requires that two oscillators disengage so that their frequencies are no longer aligned, that is, they become desynchronized; beta and mu basal ganglia rhythms, for instance, display event related desynchronization prior to movement, with sustained suppression while movements are executed [22]. Desynchronization necessarily entails a discretized segregation of the oscillators, that is, a qualitative separation of the two that is fundamentally a non-linear dynamical bifurcation [23]. Synchronization and desynchronization thus help the brain to achieve reliability or stability of outcome, as well as the flexibility to achieve varying needs, which must also be contextualized to global operation, that is, functionally salient outcomes for the 'good' of the whole individual.

The Theory of Weakly Coupled Oscillators, accordingly, captures the need for modest coupling between oscillators else they could not recombine; mathematically, this is described by the Adler equation. Weak thus means that interactions lead to phase adjustments without strong perturbations of the oscillatory generative mechanisms. The Adler equation includes terms for divergence, which are ascribed to detuning, due to intrinsic frequency differences between oscillators, and for merger, determined by the coupling constant, which is related to the sine function of the phase angle difference. Weak coupling, hence, necessarily includes the presence of diverging tendencies; the balance between these two opposing factors thereby determines the trajectory undertaken toward synchrony. Because phase locking, understood as the constancy of the instantaneous phase relation, is typically never fully achieved, phase precession generally traverses all phase angles and coupling strength continually changes throughout the phase precession cycle. Due to the presence of both merging and diverging forces, the attractive pull is enhanced when phase tuning is more proximate and reduced when widely separated, that is, the fraction of cycle time spent in phase proximity is greater than that when separated, a circumstance that is increasingly asymmetric as phase locking values approximate to 1. Worded otherwise, phase precession is slowest when phase angles are closely aligned and fastest when farthest apart.

The mechanism of weak coupling described by the Adler equation is further revealed in the fine structure of oscillator composition. This structure is apparent in mass recordings like the EEG, seen as a temporal variability in rhythmic neural activity termed phase variance, which has been linked to the individual behavior of micro-oscillators [24]. Such activity displays considerable 'noise' induced variation and has been shown to be due in part to intraneuronal temporal variation in spike production [25], occasioned by single neuron current injection, and to variability between groups of neurons that are linked within oscillatory circuits. Temporal variation observed in a mass recording like the EEG is thus indicative of a large set of micro oscillators whose alignment is stochastically determined. Set members, accordingly, generally exhibit a normally distributed phase variation. However, complicating this conclusion are observations of intermittency in phase alignment. Micro oscillators, in fact, are not simply normally distributed, but, rather, regularly display intermittent episodes of desynchronization, where they are no longer aligned with the oscillating phase [24]. The probability of this desynchronization is seen to occur in inverse relation to its duration, that is, short quick desynchronizations are regularly experienced by all set members at random intervals. Micro oscillators thus exhibit considerable behavioral independence relative to the overall population.

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Prodromal Postponement: Inferences

Cumulatively, a portrait emerging from such observations, suggest a relatively asynchronous and stochastic environment embedding multiple oscillatory patterns; hence, regional oscillations, like those activated in basal motor nuclei, are likely to occur sparsely and to be probabilistically determined [20,26]. Plausibly, the etiological factors responsible Parkinson's, dopamine synaptopathy modify oscillatory states arising from such sparse network circumstances. Hence, within a variable range of motor performance, operational vestiges resembling this framework are retained, that is, oscillatory variation due to disease still adopts an embedded profile within a larger, relatively stochastic population.

Intuitively, the sparse synchronization model offers insight into the length of the prodromal phase, where dopamine levels are significantly depleted and where the presence of Lewy Bodies and compromised synaptic architecture do not significantly impact 'normal' oscillatory profiles or motoric behavior during this phase of PD. In a stochastic field, for example, information transmission can be effected with lesser input than coupled circuits, such as that occasioned by passive spread, synaptic depression or similar mechanisms.

Regulatory influences over cortical information transmission, further, can be effective with lesser synaptic control for similar reasons. Indeed, dopamine is proposed to regulate the penetration of cortical rhythms entering the motor nuclei [2], where cortical inputs that drive events through the ganglia, notably, pass through a striatal hub prior to their entry to the basal ganglia, and where they are transformed into complex resonances. Model studies of the subthalamo-pallical network, for instance, exhibit multiple rhythms in response to cortical β input [27], suggesting that intrinsic mechanisms within these nuclei are not exclusively tied to the transmission of cortically determined frequency ranges. Indeed, select frequencies vary depending on the motor response, like 20 Hz for grip force slowing and 5 and 10 Hz for finger tapping [9]. In PD, moreover, some cortical rhythms successfully penetrate the basal ganglia, while still others are transformed or blocked [22]. Hence, dopamine may be required to regulate some, but not all, cortical input.

Regulating cortical access, on the other hand, may not fully consider other roles played by dopamine, or by the sparse network model in PD, which is only impacted after a lengthy latent phase. Increasing evidence suggests that dopamine function is not limited to that of inhibiting oscillatory penetration. For example, dopamine depletion in rats strongly affects learning-related patterning of fast spiking interneuron groups and striatal projection neurons. Dopamine loss, moreover, also affects recollection by diminishing the ability to retrieve encoded information needed for recall of motor tasks [28]. How dopamine may facilitate coding of cortical rhythms in sparse circumstances is uncertain, but could entail phase coding adjustments to non beta oscillation resonances such as those observed between cortical and subcortical zones. With sufficient spatial discrimination [22] information transfer would be limited to discrete oscillator pockets, a circumstance for which only low levels of transmitter would be needed for coding variability.

Hence, unlike the off/on gating proposed for beta oscillation, which may be occasioned through phase interference, encoding the selection and processing of cortical transmission may constitute a second and equally significant but focally directed role for dopamine regulation. Significantly, the resident oscillator field is not unimodal, but represents a complex distribution of oscillator attractors determined by network connectivities and described by the physical parameters that give rise to them. Cortical input here may synchronize with only subset of the field population of oscillators and may do so only if the relative synchronizing tendencies between them are energetically preferred to other oscillator combinations [29], a circumstance that would be facilitated in coding. For example, an important class of oscillator synchronies entails those between globally distributed and regionally entrained ones

Conclusion

Broader issues surrounding the relationship between cellular pathologies and cognitive diseases are complicated by the intrinsic complexity of cognition 'which overlays lesser but nonetheless complex metabolic structures. Information transmission and global regulation have only recently moved beyond Hodgkin Huxley single cell understandings to explore how these processes influence network architectures at micro and macro scales [20]. Current studies indicate that these are likely to constitute an increasing maze across a hierarchical continuum for which non-linear dynamics are fundamental functional features. Organismal demands for viability can be expected to dictate the architectural form that must satisfy autonomous and highly varied behaviors. The relatively focused cellular pathology and the more restricted functional operation that is impacted in Parkinson's Disease offer unique opportunities among the degenerative cognitive diseases for investigating a cognitive function that nonetheless remains highly complex.

Bibliography

1. Udupa K and Chen R. "The mechanisms of action of deep brain stimulation and ideas for the future development". *Progress in Neurobiology* 133 (2015): 27-49.

2. Brittain JS and Brown P. "Oscillations and the basal ganglia: motor control and beyond". *NeuroImage* 85.2 (2014): 637-647.

3. Bridi JC and Hirth F. "Mechanisms of α-synuclein induced synaptopathy in Parkinson's disease". *Frontiers Neuroscience* 12 (2018): 80.

4. Shreve LA., *et al*. "Subthalamic oscillations and phase amplitude coupling are greater in the more affected hemisphere in Parkinson's disease". *Clinical Neurophysiology* 128.1 (2017): 128-137.

5. Buzsaki G. "Rhythms of the Brain". New York: Oxford University Press (2006).

6. Wiesel TN and Hubel DH. "Single cell responses in striate cortex of kittens deprived of vision in one eye". *Journal Neurophyssiology* 26 (1963): 1003-1017.

7. Buzsaki G and Draghun A. "Neuronal oscillations in cortical networks". Science 304.5679 (2004): 1926-1929.

8. Singer W and Gray C. "Visual feature integration and the temporal correlation hypothesis". *Annual Review Neuroscience* 18 (1995): 555-586.

9. Timmermann L and Florin E. "Parkinson's disease and pathological oscillatory activity: Is the beta band the bad guy? New lessons learned from low-frequency deep brain stimulation". *Experimental Neurology* 233.1 (2012): 123-125.

10. Krack P., *et al*. "Five year follow up of bilateral stimlation of the subthalamic nucleus in advanced Parkinson's disease". *New England Journal Medicine* 349.20 (2003): 1925-1934.

11. Dijkstra AA., *et al*. "Evidence for imune response, axonal dysfunction and reduced endocytosis in the substantia nigra in early stage Parkinson's disease". *PLoS ONE* 10.6 (2015): e0128651.

12. Bereczki E., *et al*. "Synaptic markers of cognitive decline in neurodegenerative diseases: a proteomic approach". *Brain* 141.2 (2018): 582-595.

13. Keane PC., *et al*. "Mitochondrial dysfunction in Parkinson's disease". *Parkinson's Disease* (2011): 716871.

14. Kalia LV and Lang AE. "Parkinson's disease". *Lancet* 386.9996 (2015): 896-912.

15. Venda LL., *et al*. "Alpha synuclein and dopamine at the crossroads of Parkinson''s disease". *Trends in Neuroscience* 33.12 (2010): 559-568.

16. Perez G., *et al*. "A role for alpha synuclein in the regulation of dopamine biosynthesis". *Journal Neuroscience* 22.8 (2002): 3090-3099.

17. Lundblad M., *et al*. "Impaired neurotransmission caused by overexpression of synuclein in nigral dopamine neurons". *Proceedings National Academy Science USA* 109.9 (2012): 3213-3219.

18. Nemani VM., *et al*. "Increased expression of alpha synuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis". *Neuron* 65.1 (2010): 66-79.

19. Lowet E., *et al*. "Quantifying neural oscillatory synchronization: a comparison between spectral coherence and phase-locking value approaches". *PLoS ONE* 11.1 (2015): e0146443.

20. Wang XJ. "Neurophysiological and computational principles of cortical rhythms in cognition". *Physiological Review* 90.3 (2010): 1195-1268.

21. Pierce J. "An Introduction to Information Theory: Symbols, Signals, and Noise". New York: Dover Publishing (1981).

22. Little S and Brown S. "The functional role of beta oscillations in Parkinson's disease". *Parkinsonism Related Disorders* 20.1 (2014): S44-S48.

23. Schoner G. "Development as change of system dynamics: stability, instability, and emergence". In Toward a Unified Theory of Development. Spencer J, Thomas MSC, McClelland JL Oxford: Oxford University Press (2009)

24. Ahn S and Rubchinsky LL. "Short desynchronization episodes prevail in synchronous dynamics of human brain rhythms". *Chaos* 23.1 (2013): 013138.

25. Ermentrout GB., *et al*. "The variance of phase-resetting curves". *Journal Computational Neuroscience* 31.2 (2011): 185-197.

26. Li YX., *et al*. "Modeling N-methyl-D-Aspartate-induced bursting in dopamine neurons". *Neuroscience* 71.2 (1996): 397-410.

27. Ahn S and Rubchinsky LL. "Potential mechanisms and functions in intermittent neural synchronization". *Frontiers Computational Neuroscience* 11 (2017): 44.

28. MacDonald AA., *et al*. "Differential effects of Parkinson's Disease and dopamine replacement on memory encoding and retrieval". *PLoS ONE* 8.9 (2013): e74044.

29. Friston K. "Free energy and global dynamics". In Principles of Brain Dynamics: Global State Interactions. Rabinovich MI, Friston KJ, and Varona P (Eds) Cambridge, MA: MIT Press (2013).