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Commentary

Parkinson's Disease Motor Disorganization and Temporal Processing

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Motor control is essential for everyday life and highly contributes to the development and organisation of higher cognitive functions. Embodied cognition endemically approaches cognitive activities, grounding on sensory-motor processes and the ability to switch from each other in response to specific context and situations. In this view, it is possible to deliberate higher functions such as "expertise" and "decision making" as the ability to reactivate, deconstruct and reconstruct different motor plans in their subroutines to plastically react to external or internal environmental requirements (Leisman, Moustafa & Shafir, 2016).

Automation is the best way through which different neural patterns work to execute motor skills. A sequence of motor acts could be successfully and efficiently executed when sensory-motor associations are acquired and timed to relate each other to a specific outcome. Skills derive from the possibility to perform motor acts in sequences after the establishment of the sensory-motor rules in terms of temporally associated outcomes, and then disrupt it in subroutines and reconstruct it in different ways supporting many motor strategy, something known as plastic behaviour (Kim & Hikosaka, 2015; Liljeholm, Dunne & O'Doherty, 2015). On the contrary, a failure to predict sensory consequences of one's actions may underlie agency disturbances characterising many psychotic symptoms (Takkar, Diwadkar & Rolfs, 2017).

Such a comprehensive knowledge about intimate sensory-motor processing and higher functions was compelled by important studies aimed to clarify the motoric organisation of movements, their sequencing, and the temporal attributes (Wu, Hallett & Chan, 2015). Movement disorders are characterised by impairments spreading from hypokinetic disorders characterized by poverty of movement up to include hyperkinetic disorders associated with abnormal, involuntary movements (Dickson, 2018). On the other hand, psychiatric disorders share many symptoms and common aetiological factors with movement disorders, suggesting a degree of common or overlapping pathogenic mechanisms (Patel, Jankovic & Hallett, 2014; Peall et al., 2017). Psychiatric symptoms are part of the clinical spectrum of movement disorders and often are the premotor symptom of the disease, such as Huntington disease or Parkinson's disease (PD) (Williams-Gray & Worth, 2016; Asakawa et al., 2016). Postural and locomotor impairments of PD develop when degeneration of the dopamine (DA) releasing cells in *Substantia Nigra pars compacta* induces a near complete loss of DA in striatal tissue (Schapira, Chaudhuri & Jenner, 2017).

In patients with advanced PD, the substitutive therapy is accomplished through L-DOPA administration, providing a long-lasting improvement in motor abilities. When the loss of DA nerve terminals is almost complete, the DA striatal supply depends on the plasma level of L-DOPA. Unfortunately, the therapeutic window of L-DOPA narrows during the progression of PD with the development of L-DOPA-induced dyskinesia (LID) and a spectrum of abnormal involuntary movements (Stefani, Pierantozzi, Koch, Galati & Stanzione, 2010; Cenci, 2014). Despite recent progress, the pharmacodynamics, presynaptic and postsynaptic pathogenesis of LID is still unknown. It is hypothesised that both alteration in the regulation of DA release and clearance and neurovascular mechanism acting during L-DOPA treatment are related with LID pathogenesis (Hirano et al., 2008; Brehm et al., 2015).

It is worthy to note that motor complications are characterised by dysfunctions in temporal processing (Harrington & Rao, 2015; Avanzino, Pelosin & Vicario, 2016). PD is characterised by an increased of brain oscillatory activity in the β band range (12–35 Hz), and new bursts of pathologically synchronised activity seem to

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be associated with delayed or impaired conscious movement (Little & Brown, 2014). The development of LID is accompanied by opposite effect on the β band and largely increasing the γ band frequency (60–80 Hz) (Salvadè et al., 2016).

Therapeutic interventions such as the deep brain stimulation or DA continues therapies are used to manage the motor fluctuation deriving from the long-lasting L-DOPA therapy and to suppress pathologically synchronised oscillations. In the unilaterally 6-OHDA lesioned rat, the repeated administration of DA agonist, apomorphine, induces an exacerbating repetitive, evolving into a compulsive, behaviour that probably is dependent on a disruption of the temporal coherence of the pre-frontal cortices deriving from the two hemispheres (Wu et al., 2015; Florio, 2017).

In impulse motor control deficits, in which explicit temporal constraints are needed, an impaired inhibitory role of pre-motor-basal ganglia dysfunction (subthalamic nucleus, hyperdirect connecting pathway) is hypothesised (Graybiel & Smith, 2016). Alternatively, it is supposed that temporal coding, needed to inhibit inappropriate motor acts, are missing because of the prefrontal cortex-basal ganglia dysfunction (Gu, van Rijn & Meck, 2015). Temporal processing occurs across different timescales. Millisecond timing is referred to speech perception and motor control, whereas milliseconds to minutes timing is important for computational learning and decision-making. In addition, cycling reoccurring stimuli can be predicted in their temporal sequence if motor movements define the duration. As a consequence, two-timing systems were proposed that engage different neuronal circuits, one that is automatic and another that is cognitively controlled (Avanzino et al., 2016).

Undoubtedly, switching between automatic and voluntary controlled movements is a function of basal ganglia (Florio, Confalone, Sciarra, Sotgiu & Alecci, 2013). Switching movements throughout different scale of time is the prerequisite through which it is possible to organize motor behaviour in response to significant environmental stimuli. We can conclude that any imbalance between sequencing and temporal processing involves impairment in the possibility to organise behaviour from the subtle and accurate imagery of thinking to the perfect execution of skilled movement, resulting in both movement and cognitive impairment.

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