

The Torque3 Platform and Parkinson's Disease Overview and Hypothesis

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Parkinson's disease is a brain disorder characterized by unintended or uncontrollable movements, such as shaking, stiffness, and difficulty with balance and coordination. Other manifestations of Parkinsonism can include insomnia, depression, cognitive impairment, dementia, and psychosis. Symptoms usually begin gradually and worsen over time. The primary modality of treatment is medication designed to address the Dopamine deficiency caused by a loss of cells in the substantia nigra, deep within subcortical regions of the brain. The substantia nigra is robustly connected with the basal ganglia, or striatum. These deep structures are interconnected with the thalamus, cortex, and cerebellum to create small and large-scale neural networks that serve numerous functions.

In Parkinsonism, disruption in these networks lead to impairment in both movement and cognitive functioning in dramatic ways. There is increasing evidence that executive functions and attention are associated with gait and balance, and that this link is especially prominent in older individuals or those who are afflicted by neurodegenerative diseases, such as Parkinson's disease, that affect cognition and/or motor functions (Wu, et al, 2011). Rather than simply being a disorder of one small part of the brain, Parkinsonism can be conceptualized as a disorder of disrupted connectivity between the multiple brain regions involved in movement and cognitive function.

Current Interventions:

The mainstay of treatment for Parkinsonism is the use of medications that replace Dopamine or enhance the Dopaminergic system. Physical therapy is also an important part of current therapy. While it does not eliminate the core pathology, physical therapy and physical exercise may maximize motor capabilities and enhance the quality of life. For example, Parkinsonian gait disturbances can be reduced by different types of physical exercise, such as walking on a treadmill and stationary biking (Li et al 2021). There is substantial evidence that physical exertion, both moderate and demanding, can improve motor function and simultaneously improve cognition, executive function, motor learning and neuroplasticity. For example, intense cycling, with rapid cadence (or RPM) improves neural connectivity, especially in the thalamus that is densely interconnected with the basal ganglia, cerebellum, and cortex; suggesting that this increased connectivity may explain some of the improvements seen from physical exercise (Shah et al 2016). Having said that, bicycling at any level of intensity can improve motor performance of Parkinson's patients and improve crucial features of gait (Tiihonen et al 2021).

There has been a growing movement toward combining visual, and sometimes auditory experiences to enhance physical exercise and improve intensity of effort and, hopefully, improve outcomes. For example, "exergaming" integrates some degree of augmented or virtual reality (VR) with physical exercise and some sort of cognitive activity. In much of exergaming, what is called "VR" is simply flat screen video with an auditory component. This is often called "non-

immersive” VR. Interventions that include a more substantial sensory experience incorporate VR headsets and headphones. This is generally called “immersive” VR. Current evidence that both so-called non-immersive and immersive VR can enhance physical therapy in numerous ways and can improve outcomes in gait - both step and stride length (Dockx et al 2016), balance (Yu, et al 2023, Lei et al 2019, Cieřlik et al 2023), activities of daily life, and quality of life (Yu, et al 2023).

Both immersive and semi-immersive models have shown significant cognitive improvements, including executive functioning, compared to conventional rehabilitation (Marotta et al 2022). Exergaming has been shown to result in better outcomes compared to control groups as demonstrated by several tests, including: Timed Up and Go test, 5 times Sit-to-Stand test, the Short Physical Performance Battery, the Go/No-Go test and in the Delis-Kaplan Executive Function System test (Grospretre et al 2023, Cieřlik et al 2023, Jäggi et al 2023).

However, while there is a cognitive component to exergaming, it is merely intended to enhance the impact of physical therapeutic exercises as they are currently conducted. Few, if any, interventions combine physical exercise activity with intense cognitive interventions that purport to be *therapeutic in and of themselves* (Nadeau et al 2017). This is where the Torque3 platform, the Outbounder ARS, offers something new. The Outbounder ARS can potentially provide a novel treatment that *simultaneously* engages all aspects of motor and neurological functioning while engaging in therapeutic exercise. We believe that our system has the potential to induce cortical and subcortical neuroplastic changes that exceed those previously documented.

The Outbounder ARS

Torque3 has developed a robotic assisted deeply immersive simulator that engages a patient's muscles, senses, and cognitive abilities during treatment. Our platform, called the Outbounder ARS, simultaneously engages all aspects of sensory and motor systems and recruits all brain regions that play a role in visuospatial perception, attention control, motor planning and action, threat detection, enjoyment, fun, emotional experience, and reward/satisfaction. As discussed above, Parkinsonism is characterized not only by a Outbounder ARS is specifically intended to activate these networks in powerful ways.

It activates regions related to Parkinsonian impairment including:

- (1) Frontal cortical systems responsible for executive functions, attending to spaces bilaterally, planning, and sequencing thoughts and actions.
- (2) Supplementary and Primary Motor cortical systems responsible for planning and initiating motor activity.
- (3) Amygdala that constantly scans the environment for potential challenges, threats, or risks that influence decision making and motor activation.
- (4) Dorsal Striatum that plays a key role in organizing motor activity.
- (5) Ventral Striatum that plays a key role in reward, pleasure, and fun.
 - * Note, both the Dorsal and Ventral Striatum are robustly interconnected with the Dopamine producing substantia nigra.
- (6) Brainstem centers that produce Norepinephrine and Dopamine neurotransmitters, including the Substantia Nigra.

- (7) Limbic system that elaborates upon emotions and places experience in the context of space and time.

We recently conducted 2 Functional Assurance Evaluations (FAEs) that established the safety and reliability of the system. The assessment participants included 6 individuals with hemiplegia and cognitive impairment related to stroke, tumor, traumatic brain injury, surgery, and cerebral palsy. These participants were administered several tests for cognitive, mental, and physical functioning before, during, and after the FAE. While the participant evaluations did not rise to the level of an academic clinical study, certain findings suggest that the Torque3 platform engages the brain in ways currently unavailable in traditional neurorehabilitation.

The key findings from the 2 FAEs are:

Psychologically:

- Depression – decreased or eliminated
- Anxiety – decreased or eliminated

Physical Therapy assessments showed some improvements in:

- Gait
- Balance
- Postural Stability
- Fall Risk
- Lower Extremity Strength
- Increased Endurance
- Sensory Perception
- Range of Motion
- Decreased intention tremor
- Decreased pain related to exercise

Cognitive findings revealed improvements in:

- Speed of neural reaction
 - Simple Reaction Time
 - Choice Reaction Time
- Spatial Perception
- Perseveration (motor and cognitive)
- Overall cognitive functioning (Montreal Cognitive Assessment, MoCA)

Hypothesis:

We hypothesize that due to its unique capabilities as described above, the Torque3 platform may play a role in the treatment of Parkinson’s Disease unlike any modality currently available. Such a hypothesis must be tested by controlled clinical investigations in academic institutions.

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