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SCIENTIFIC COMMENTARIES

Quantitative postural models as biomarkers of balance in Parkinson's disease

This scientific commentary refers to 'Balance control systems in Parkinson's disease and the impact of pedunculopontine area stimulation', by Perera *et al.* (doi:10.1093/brain/awy216).

Falls as a result of imbalance related to the axial features of freezing of gait and postural instability have a major impact upon quality of life in patients with Parkinson's disease (Soh *et al.*, 2011). Unfortunately, axial dysfunction in Parkinson's disease responds poorly to current drug and deep brain stimulation (DBS) therapies. More recently, pedunculopontine nucleus (PPN) DBS has been used to improve axial features. But despite its promise, PPN DBS remains experimental as the data concerning its effect on Parkinson's disease-related imbalance are highly variable (Thevathasan *et al.*, 2018). In typical Parkinson's disease with relatively little axial involvement, the effect of DBS (e.g. subthalamic nucleus stimulation) can be reliably assessed by quantifying limb kinematics (e.g. tremor or kinesis), providing a ready parameter for optimizing DBS parameters. A key barrier to studying the effect of PPN DBS is the lack of easy-to-obtain markers of gait and balance to reliably assay treatment effects. The availability of such biomarkers would accelerate studies of the effect of PPN DBS on postural control. In this issue of *Brain*, Perera and co-workers use quantitative postural models to derive biomarkers of balance in patients with Parkinson's disease and show that these parameters correlate with clinical measures of imbalance (Perera *et al.*, 2018).

PPN DBS studies show a consistent reduction in falls (Thevathasan *et al.*, 2018) with sustained effects for 2 years or even longer (Mestre *et al.*, 2016). One problem with measuring a reduction in falls is that its prospective nature makes for slow progress in PPN DBS research, as the data can only be used to inform subsequent studies as opposed to optimize DBS parameters at the outset of a study. A second, perhaps more critical, problem is the multifactorial and often complex nature of falls causation. Fall response to any successful treatment is non-linear, e.g. if the frequency of falls is a product of the amount of locomotor activity undertaken and the relative risk of falling when locomoting, a patient may reduce falls by walking less; or a patient with objectively improved balance may show no change in falls as they start walking more. Falls risk can be modulated by patients' lifestyle choices; e.g. if a patient regains the ability to hill walk, they may simultaneously have more falls and report improved quality of life. Thus, since there are many factors affecting gait, the small sample sizes typical of PPN DBS studies (six to eight patients) are insufficient to account for between-patient variability, particularly given the complexity of gait and its assessment. This combination of factors is one reason why the benefits of PPN DBS in Parkinson's disease are currently unclear.

Sensitive and easy-to-obtain outcome measures that independently and reliably predict fall frequency (all other factors remaining the same) are thus needed for PPN DBS studies. Freezing of gait is associated with falls (Michałowska *et al.*, 2005), and gait freezing is reduced by PPN DBS, which may reduce falls (Mestre *et al.*, 2016), although not consistently (Thevathasan *et al.*, 2018). In one blinded controlled study (Thevathasan *et al.*, 2012), PPN DBS had little effect on limb kinematics during walking, implying little utility as a biomarker of PPN DBS effect. Recently, PPN DBS was shown to improve quantitative assessment of vestibular perceptual thresholds during passive whole-body yaw rotation self-motion (Yousif *et al.*, 2016), indicating a PPN DBS modulation of higher order sensory signals that may be linked to enhanced balance. Surprisingly, there are only limited data on the impact of PPN DBS on postural stability during quiet standing. There are even less data about whether measures of postural stability predict improvement in falls with PPN DBS and there are no prior studies describing the effect of PPN on gait function with postural models.

Perera *et al.* offer the first necessary step for deriving postural signatures for use as biomarkers: they related measurement of sway during quiet standing to parameters of possible underlying computational mechanisms controlling sway. Sway data were collected from 13 healthy controls and

13 patients with Parkinson's disease implanted with PPN deep brain stimulators for severe postural instability and falls. Patients were tested OFF medication and blinded to two conditions: off and on PPN stimulation. These postural mechanisms were expressed as a simplified postural model combining biomechanical and central control systems, with the latter being the critical ingredient for stable posture. In modelling posture, the simplest approach is to assume the human body is an inverted pendulum with a single pivot at the ankle (Fig. 1). From an engineering perspective, there are two main ways of controlling this inverted pendulum to maintain an upright body posture: continuous and intermittent control (Fig. 2) (Glasauer and Straka, 2017).

For the continuous control of body posture—which requires continuous motor action—Perera *et al.* used a relatively simple controller, common in engineering practice, called a 'PID' (proportional-integral-derivative) continuous control system (Fig. 3 and Supplementary material), the parameters of which serve as possible biomarkers. In contrast to a continuous controller requiring a continuous motor action, an intermittent controller only requires motor output from time to time: for example, if the error between desired and actual state becomes too large, a corrective motor action is issued. Both types of control can coexist, an example being our gaze movements, where we can track moving objects with our eyes (continuous control) or make rapid saccades (intermittent control) to catch up with the target if lost during ocular pursuit. Unlike their use of an explicit model for the PID controller, Perera *et al.* did not explicitly model intermittent control but simply looked for its signature in sway patterns. Specifically, intermittent control of posture would predict discontinuities in the sway pattern and here, the outcome of interest for the authors was the number of discontinuities in the sway pattern that occurred over time (i.e. the frequency of intermittent switching).

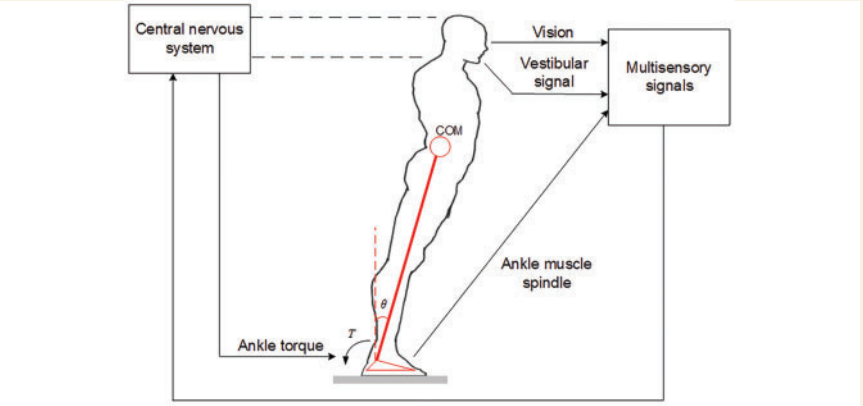

Figure 1 Conceptual engineering control system models of quiet standing sway in humans. The simplest postural control model of a quietly standing body assumes a pivot around the ankle as if the body were an inverted pendulum where the centre of mass (COM) of the body is above the ankle pivot point. An inverted pendulum is inherently unstable and will fall over without additional help. The system controlling upright posture is conceptualized as a central neural command output to the muscles that generate an appropriate torque at the ankle, T, in response to a sensory signal indicating the body sway angle, θ, from the upright, and hence maintains the body close to upright. Note that computational models of human movement and balance are conceptual and attempt to predict the spontaneous motor (or sway) behaviour rather than explicitly reflecting neuroanatomically correct control mechanisms.

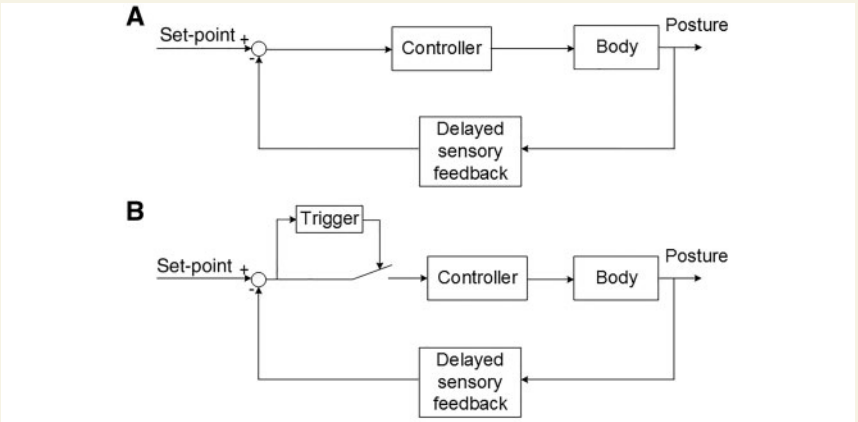

Figure 2 Feedback control mechanisms for human posture. (**A**) Continuous control: the sensed posture is compared to the set-point (zero for quiet standing), and their error is sent to a controller, which computes optimal motor commands for error minimization. The time delay in the sensory feedback severely degrades the stability of the continuous control loop. (**B**) Intermittent control: the simplified scheme here is similar to **A**, except that a switch prevents error signals from being transmitted to the controller such that the latter acts only if the trigger closes the switch when the error between the set-point and sensed posture exceeds a threshold. This model essentially assumes that postural control mechanisms are effectively switched off in the vertical position but when the body moves away from the near vertical, postural control mechanisms are switched back on. Compared to continuous control, the intermittent control is more robust to the feedback time delay.

Perera *et al.* found abnormal gains in the continuous (PID) control model and reduced intermittent switching. Additionally, PPN DBS improved the degree of intermittent switching, PID control gains, and clinical balance score towards normal. Indeed the clinical balance score, an amalgam

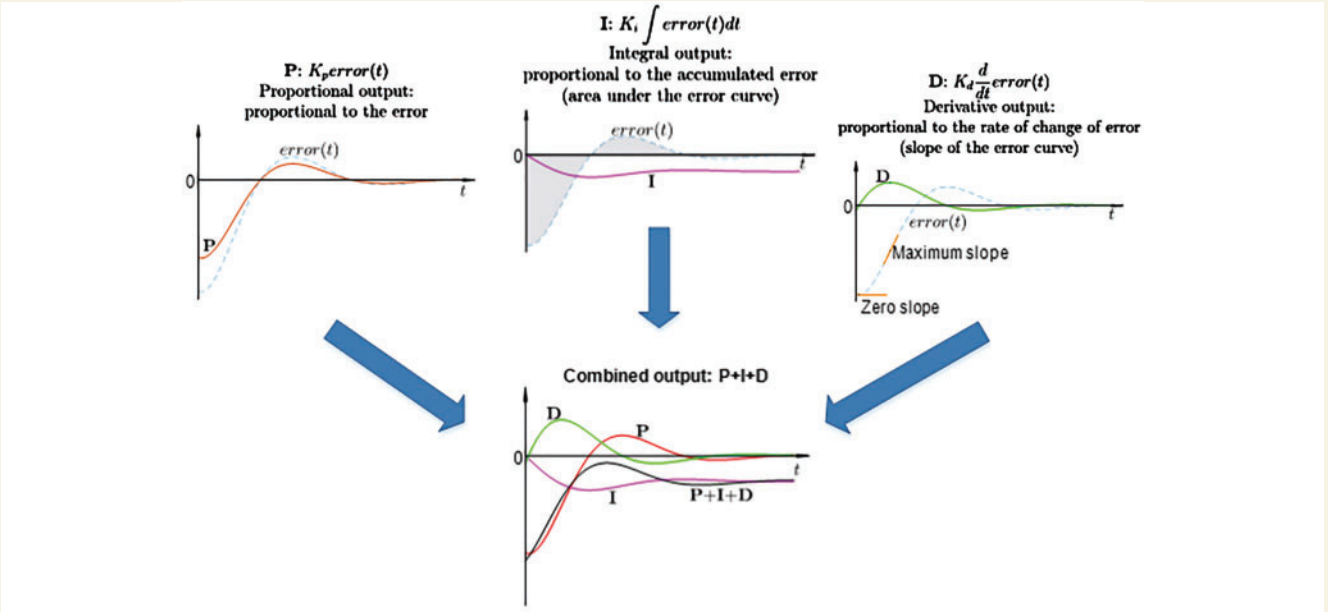

Figure 3 An example of the input and output signals of a PID control system, which is commonly used in engineering practice. A PID control system consists of three basic controllers, proportional (P), integral (I), and derivative (D) controllers, within which the control gains, K_p, K_i, K_d, are varied to stabilize the controlled plant to optimise the response. Each of the 'P', 'I', 'D' controllers has the same input, the angular error signal between the upright and the sensed human body attitude, but differ in the outputs to serve different purposes. The output of the 'P' controller (*top left*) is proportional to the value of error with K_p and provides the ankle with the stiffness for correcting instances of sway angle. A large K_p results in a large output, while a small K_p results in a small output, hence a less sensitive controller. The 'I' controller (*top middle*) accounts for past values of error and integrates them over time to give the accumulated offset that should have been corrected previously, and thus eliminates the residual steady-state error that occurs with a 'P' controller. Its output is the multiplication of the accumulated error (the shaded area) and K_i. A large K_i can cause the overshooting of the human body direction. Outputting the multiplication of K_d and the slope of the error curve (e.g. the orange lines), the 'D' controller (*top right*) predicts the trend of error and thus reduces setting time and overshoot. A large K_d can amplify high frequency noise, yielding large amounts of change in the output. It is known from control system theory that the combination of 'P' and 'D' controllers is enough to stabilize an inverted pendulum, and the 'I' controller is not necessary for stability but is for eliminating the steady-state error. The sum of outputs of 'P', 'I', and 'D' controllers (*bottom*) forms the final output of the PID control system. The simulation—provided in the Supplementary material—shows the effect of controlling a single inverted pendulum by a controller using only 'P' 'I' or 'D' compared to a PID controller with appropriate (proper) and inappropriate (improper) gains.

of the Unified Parkinson's Disease Rating Scale (UPDRS) chair rise test (a rating of attempts to rise from sitting) and the pull test (which measures postural reflexes to a postural perturbation when standing), correlated well with intermittent switching of postural sway and PID control gains (see Figure 5 in Perera *et al.*, 2018), implying that the control system metrics may have potential as biomarkers of balance impairment in Parkinson's disease. Intriguingly, Perera *et al.* found no correlation between the rostrocaudal distance of the PPN stimulation location (one factor amongst many that may explain variability in the clinical response to PPN DBS) and intermittent switching or clinical balance score. This finding alludes to the use of postural biomarkers for targeting DBS, or indeed suggests a network explanation for the effect of PPN DBS (a discussion of which is beyond the scope of this commentary).

Of course, behavioural testing in patients is challenging, as investigators must ensure laboratory testing is not too onerous, particularly as patient volunteers are typically highly motivated. It follows that there is always room for methodological improvement in patient-based studies, including those using postural models as biomarkers. For example, Perera *et al.* used the reaction time from a volitional elbow flexion assuming that it reflected the feedback time delay in the continuous PID postural control model. Perhaps more appropriate would be to estimate the model's feedback delay directly from the data as this would require fewer assumptions (Hidenori and Jiang, 2006). Perera *et al.* also analysed the two types of control systems independently; however, a more parsimonious approach would be to assess PPN DBS responses with a combined continuous-intermittent controller model. Indeed, when using a combined continuous and intermittent controller to control posture, lengthy feedback delays—inherent to long axons bringing afferent signals from the lower limbs—assume a lower importance in achieving postural stability (Asai *et al.*, 2009).

Despite its current experimental status, investigators continue to explore the use of PPN DBS in patients with Parkinson's disease given the impact of falls upon quality of life (Soh *et al.*, 2011), and the lack of alternative

treatments for axial dysfunction in these patients. However, biomarkers with good predictive power for assessing quality of life related to mobility and global gait functioning are critical to establish the clinical utility of PPN DBS. Using these postural biomarkers to optimise DBS parameters for balance performance post-surgery, may accelerate the pace of research. Additionally, future PPN DBS studies will not only need to measure falls frequency prospectively, but also obtain overall locomotor activity during daily life (via wearable devices) which will allow investigators to obtain an index of falls risk per quantum of locomotor activity. Signal analyses could also allude to the type of activity involved when the fall occurred, e.g. some patients may fall during quiet standing while others may fall during more vigorous activity. It follows that such complex analyses require much larger studies than those already completed. The recent publication of the PPN DBS working group consensus (Thevathasan *et al.*, 2018) is a step in the right direction for developing large-scale multicentre studies; however, choosing reliable outcome measures, in addition to accepting the complexity of assessing gait and falls outcomes, must be part of the calculation in powering future studies. The analysis via modelling of biomechanical control systems in patients is a promising tool for deriving hallmarks of postural performance. Its use for disease monitoring including response to treatments, from PPN DBS to rehabilitation, indicates a utility that extends far outside the realm of PPN DBS but includes other groups such as the healthy elderly.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Stimulating cingulate: distinct behaviours arise from discrete zones

This scientific commentary refers to 'Motor and emotional behaviours elicited by electrical stimulation of the human cingulate cortex', by Caruana *et al.* (doi:10.1093/brain/awy219).

The cingulate cortex is one of the most commonly described loci of dysfunction in psychiatry and neurology, and as regions of the brain go, its functional properties have stirred considerable controversy amongst neuroscientists (Ebitz and Hayden, 2016). Such debates have even led to the region having its own social media hashtag (#cingulategate). Why such controversy? The answer to this is multifaceted but two key factors are (i) most of the theoretical accounts of cingulate function are based on informative but correlational neuroimaging data; and (ii) although appearing by eye to be a continuous piece of tissue, the cingulate cortex in fact comprises