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Addressing the challenges of clinical research for freezing of gait in Parkinson's disease

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A recent *Scientific Panel Discussion* led by the Scientific Issues Committee of the International Parkinson and Movement Disorder Society has concluded that a 'systems biology' strategy should be implemented to advance our understanding of the pathophysiology underpinning gait and balance disorders in Parkinson's Disease (PD). Critically, the failure to appreciate the neurobiological processes associated with these

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challenging symptoms is seen as the most significant barrier to the development of more successful therapeutic approaches.

The *Scientific Panel* has also proposed that there should be a focus on the development of testable experimental models probing the interacting circuits and networks that control gait and postural balance (see details[1]). Utilizing advanced technologies, these models would address discrete mechanistic hypotheses, which could then be evaluated in a human testing phase with adaptive paradigms to validate clinical pathophysiology. However, such successful research would rely on the rigor and quality of large datasets from multiple centres with investigators adopting a coordinated and standardised methodology. Such a program of research would need to be very carefully considered, especially in the clinical setting. Therefore, there is a pressing need to establish a complementary clinical framework addressing major issues such as definitions, assessments and measurements, as well as identifying other useful approaches that would facilitate a systems biology approach or indeed inform the experimental modelling on the emerging clinical observations through a reversed translational approach. This Viewpoint represents our recommendations on clinical research, and whilst not exhaustive is intended to help steer the community's activities in this endeavour.

Of Mice and Men…

Creating eloquent pre-clinical models to interrogate the pathophysiology of gait and balance problems is clearly a very appealing concept that could lead to fresh insights and novel therapies. However, one must consider some of the limitations that exist in translating these observations into clinical practice. The neural control of gait and balance is not well understood in humans, and whilst it has been possible to elucidate more of these details in animal models, the development of freezing of gait (FOG) and imbalance in PD models has been challenging. Indeed, it should be appreciated that by their very nature, these events are paroxysmal, rather than manifesting as a continuous disturbance and hence are difficult to duplicate. Nevertheless, loss of balance and falls can be reproduced in rodents and primates, and FOG is present in primates with moderate to advanced parkinsonism[2, 3]. A challenge still remains to validate the data derived from these models, which critically relies on matching experimental and human testing. For example, the cholinergic system has been implicated in the falls of parkinsonian rodents[4] and a loss of the cholinergic projection from the Nucleus Basalis of Meynert (NMB) may be predictive of progressive gait disturbances in PD[5], but it is not clear if this relates to its role in locomotion, attention or both.

In addition to the importance of translating the model findings to the clinical setting, another major topic for consideration relates to the extension to which the clinical data can contribute to refining the animal models, underscoring the need for bidirectional translation. From our current understanding of events like FOG, it would appear that they are probably related to a temporary overload that is triggered across a complex network of related neural nodes that ultimately converge on a final common pathway resulting in gait arrest[6]. Clearly, the application of systems biology strategies that can converge multiple analyses of data may help to build up such theoretical frames, and thereby afford valuable information to the experimental testing. The challenge of modeling is further complicated by the existence of

clinical heterogeneity where seemingly related phenomena, such as the differing phenotypes of FOG (e.g., trembling in place, shuffling with small steps, and complete akinesia)[7], and varied response to dopaminergic therapy may point to distinct pathophysiologies.

Great Expectations…

Despite these potential barriers, there are many promising avenues where clinical research could offer valuable insights. Indeed, to paraphrase Otto von Bismarck, perhaps clinical translation (rather than politics) should be regarded as the art of the possible. The *Scientific Panel* recommended a multi-modal approach to data gathering to draw inferences from multiple interacting systems. If appropriately resourced, it would be feasible to collect such a detailed dataset within well characterised groups of patients. Indeed, previous studies have demonstrated the potential role for structural (e.g., volumetry[8], diffusion tensor imaging[9], neuromelanin[10]), functional (fMRI[11], PET[12]), electrophysiological (DBS[13], EEG[14], TMS[15], tDCS[16]), and kinematic (accelerometry[17], pressure mats[18]) techniques combined with clinical phenotyping to test hypotheses. However, this reductionist approach often offers only limited insights into underlying pathophysiology, such as monitoring activity in the output regions of the basal ganglia through DBS recordings. Clearly, such information would be greatly enhanced by combining techniques, such as collecting simultaneous surface EEG and functional neuroimaging. Additionally, methods are now available, such as graph theory, to look at the whole brain simultaneously with functional methods including fMRI and EEG. Most past studies have explored one part or one connection of the brain dealing with a focused hypothesis. Now multiple interacting networks can be studied at the same time, which will allow a more integrated view of the brain as a complex system.

Prospective longitudinal studies in a significant number of patients combining these approaches in a standardised dataset would represent a major opportunity for people working in the field. Ideally, this comprehensive information would be shared as a de-identified resource, supplemented by willing researchers agreeing to upload an agreed minimum dataset from their ongoing studies. Indeed, thought could be given to the collection of such data from a nested trials approach[19], where patients participating in one particular study would agree to some of their data being shared as part of a larger, longitudinal registry for use by the international community.

It could be argued that much of our knowledge about gait and balance disturbances represents correlational observations rather than providing a clear understanding of the underlying neurobiology. However, this information is still highly valuable and should help shape some of our future thinking. For example, whilst pre-clinical experiments manipulating selective neurotransmitters may prove highly informative, one must consider how this would be translated into patients who have concurrent pathologies and multiple pharmacotherapies. Recent work has already highlighted that the withdrawal of anticholinergics in PD patients can lead to significant improvements in FOG and falls over 12 months[20]. In addition, an ongoing Phase III study (CHIEF-PD NCT04226248) is currently evaluating the impact of cholinesterase inhibitors on falls risk in PD following the earlier significant findings of a Phase II study[21]. Thus, one could envisage such clinical studies being coupled with additional assessments (e.g., PET, fMRI, fNIRS, DBS

monitoring) to test mechanistic hypotheses. Furthermore, it should be possible for clinical researchers to construct experiments that better target our understanding of the neural mechanisms involved. For example, the relationships between FOG and impaired balance are not well appreciated but previous studies have observed the link between FOG and hypometric anticipatory postural adjustments (APAs), which normally trigger the stepping program to facilitate gait[22]. Thus, future experiments could be constructed to evaluate these relationships, such as by performing gait studies where ceiling track systems could offer variable weight support to patients to determine the contribution of postural reflexes to freezing[23]. Furthermore, given the growing literature about the role of anxiety as a trigger of FOG[24, 25], consideration should be given to combining such studies with autonomic measures, such as heart rate and skin conductance.

Before embarking upon a more integrated program of research, the clinical field needs to address a couple of major but soluble issues, namely the standardisation of definitions and the objective measurement of symptoms. This is particularly true in relation to FOG, where the current definition of the phenomenon lacks clear guidance and includes terms such as *brief*, *episodic,* and *marked reduction* without quantifying these observations[26]. Furthermore, the current definition is moot on the differing phenotypes of gait freezing that have been described in relation to lower leg movement[7] and does not consider non-gait freezing[27] or how FOG may be different in non-PD patients[28, 29]. Obviously, standardising the definition of FOG is critical if researchers are going to be able to measure the phenomenon consistently. The current definition of FOG came out of the first International FOG Workshop and this group has had two subsequent conferences. Therefore, consideration should be given to convening a Delphi style panel of experts at the next Workshop to address these fundamental issues.

A standardised approach to measuring clinical phenomena is also vital if systems biologists are going to analyse reliable data from multiple centres. Again, using FOG as an example, the currently adopted gold standard for quantification is through video scoring of timed-up-and-go trials by independent experts[30]. However, different centres have used differing approaches to quantify these outcomes ranging from scoring episodes by their clinical severity/duration[31, 32], through to reporting the percentage of time spent freezing during intended walking periods[33]. Whilst the intraclass correlation coefficient between the independent raters for these studies has generally been acceptable, these scoring approaches are labour intensive, time consuming and still subject to individual variability and bias (e.g., experience of the raters and the centres). Thus, significant efforts have been made to utilise more objective measures such as through wearable devices (typically accelerometers)[34, 35] and more recently, automated video scoring algorithms[36]. Obviously, the instrumented measurement of gait and balance disturbances also offers the possibility of assessing patients in their home environment, which is highly desirable, but it is not yet clear that these systems offer sufficient accuracy in an unsupervised setting, especially for the detection of very short lived clinical events[37]. Clearly the ability to collect objective data that are accurate is imperative, and this goal could potentially be best achieved by a panel of experts working as a taskforce to validate the standardised methodologies that would then be universally adopted.

Lost in Translation…

As highlighted above, the field will need to find pragmatic ways to explore any hypotheses that arise from experimental models. There will need to be greater integration and data sharing across a variety of disciplines including engineering, basic and clinical neuroscience. Significant adjustments in our patterns of research are required for a systems biology strategy to be successful in progressing our understanding and treatment of gait and balance disorders in PD. Otherwise, important breakthroughs may be lost in clinical translation.

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Dr. Hallett is an inventor of patents held by NIH for an immunotoxin for the treatment of focal movement disorders and the H-coil for magnetic stimulation; in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health and Brainsway (both unpaid positions). He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, Wiley, Wolters Kluwer, and Elsevier. He has research grants from Medtronic, Inc. for a study of DBS for dystonia and CALA Health for studies of a device to suppress tremor.

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