Semantic Fluency Predicts Gait Velocity in PSP

Koustav Chatterjee, Supriyo Choudhury, Ummatul Siddique, Banashree Mondal, Marium U. Kulsum, Saptak Haldar, Purba Basu, Rebecca Banerjee, Hrishikesh Kumar

Department of Neurology, Institute of Neurosciences Kolkata, Kolkata, West Bengal, India

Abstract

Context: Progressive supranuclear palsy (PSP) is a large-scale network disease resulting in variable signs and symptoms including gait impairment and higher order cognitive dysfunction. Despite few studies showing the association of falls and cognitive dysfunction, the existing literature is yet to establish the exact relationship of discrete characteristics of gait with cognitive function in PSP. Aims: In this cross-sectional study, we aimed to characterize and explore the relationship of these two apparently distinct physiological phenomena in patients with PSP and across its different variants. Methods and Material: Quantitative assessment of two-dimensional gait parameters was measured using an electronic walkway (GAITRite®). Dementia Rating Scale-2 was used to assess global as well as higher order cognitive functions. Statistical Analysis Used: A regression model was used to interpret results. Results: We observed that the variability domain of gait was significantly impaired in PSP patients with severe cognitive impairment compared to that of intact cognition. Moreover, initiation/perseveration (I/P), a higher order cognitive process, and one of its specific components, i.e., complex verbal task ($\beta = 2.39, P < 0.001$), significantly predict gait velocity in PSP ($\beta (1, 40) = 16.102, P < 0.001$). Conclusions: Our findings indicate that the severity of cognitive functions affects gait variability, which might lead to frequent falls as observed in PSP. Furthermore, semantic fluency task of I/P function may act as a predictor of gait velocity. We suspect that higher order cognitive dysfunction through the damage of frontal lobe structure including dorsolateral prefrontal cortex or related network may influence gait in PSP.

Keywords: Cognitive function, gait, initiation/perseveration, progressive supranuclear palsy

INTRODUCTION

Progressive supranuclear palsy (PSP) is an age-related neurodegenerative disease. Both aging and disease pathology may contribute to the changes in different brain areas and related circuits resulting in variable signs and symptoms including gait impairment over time across different phenotypes of PSP. Gait can be represented by multiple discrete characteristics, under the influence of different neural components. As a result, it is likely to respond in a selective manner to aging and pathological conditions.[1] In addition, gait can also be modulated through brain areas responsible for higher order cognitive process or executive functions (e.g., attention and memory).[1,2] Therefore, understanding the precise nature of neural control of PSP gait by exploring the link between gait and cognition might reveal new insights of the disease process. Despite few studies showing association of falls with cognitive dysfunction, the exact relationship of specific characteristics of gait with cognitive and executive function in PSP and across its different variants is still unknown.[1] We hypothesized that specific higher order cognitive functions influence discrete gait characteristics in PSP. In this cross-sectional study, we aim to characterize the nature of gait and higher order cognitive functions in PSP and its different variants. Additionally, we want to explore the relationship between different domains of gait and cognitive functions in patients with PSP.

SUBJECTS AND METHODS

The study was approved by the institutional ethics committee and written informed consent was obtained from all the study participants. Fifty consecutive diagnosed cases of PSP patients classified into different PSP subtypes according to the Movement Disorder Society (MDS) criteria were recruited from the movement disorder outpatient department of a tertiary care neurosciences institute in India.[4] Gait analysis through GAITRite® and cognitive assessments through Mattis Dementia Rating Scale-2 (DRS-2) were done. Mattis-DRS-2 was used to examine global and different higher levels of cognitive function, i.e., attention (ATT), initiation/perseveration (I/P), construction (CONST), conceptualization (CONCEPT), and memory (MEM).[5] Motor severity was assessed using the MDS Unified Parkinson’s Disease Rating Scale part III.[6]

For quantitative estimation of two-dimensional spatio-temporal gait parameters, subjects were instructed to walk four times...
successively at a self-selected normal pace on a 500-cm long electronic walkway (GAITRite®, CIR Systems, Inc., Franklin, NJ, USA), which had pressure sensors embedded in it. Gait outcomes were represented using the gait model developed by Lord et al., 2013.[7] Based on this model, different gait parameters were distributed amongst the five gait domains, i.e., pace, rhythm, variability, asymmetry, and postural control. From each domain, five representative gait parameters (velocity, swing time, step length variability, step time asymmetry, and step width) were selected for further investigation, as all the gait parameters from a given gait domain are comparable in our study [Supplementary Table S1].

Data were analyzed using SPSS Version 20 (IBM, Armonk, NY, USA). The normality of the data was examined using Shapiro–Wilks test. Velocity, step length, and step width showed normal distribution, whereas other gait parameters and cognitive measures (total DRS score, scores of ATT, I/P, CONST, CONCEPT, and MEM) were not normally distributed. One-way ANOVA was used to determine if significant differences in mean score of parametric gait variables exist across “intact,” “mild,” “moderate,” and “severely” impaired group of PSP, whereas Kruskal–Wallis ANOVA was done to understand if significant differences in mean score on all the nonparametric gait variables exist across these cognitive categories. The number of patients in each of the subtypes other than PSP with Richardson’s syndrome (PSP-RS) and PSP with Parkinsonism (PSP-P) was negligible in our sample. Moreover, PSP-RS are the most predominant phenotype followed by PSP-P; as expected. Therefore, we decided to restrict ourselves for further analysis with PSP-RS versus PSP-P and PSP-RS versus PSP-non-RS groups. Unpaired t-test was used to compare the means for all three normally distributed gait parameters in these subtypes and Mann–Whitney U-test was used to compare the difference between the same groups for all other gait parameters and cognitive measures. Associations between all cognitive and gait measures were first examined using Spearman’s correlation followed by partial correlations, where age, disease duration, LEDD, and postural instability were used as covariates. No significant differences were noted on pairwise comparison between the left and right sides of the gait parameters. So, right-sided gait parameters were taken for further statistical comparison and data representation in tables and figure. Finally, multiple linear regression analysis was implemented to explore major determinants of gait parameters, based on the result of partial correlation. All data were reported as means and SD unless otherwise stated. P values of <0.05 were considered statistically significant for all the statistical tests.

**RESULTS**

The mean age of all 50 patients was 64 ± 7 years with the disease duration of around 3 years. Seventy two percent of the patients was male. As expected, PSP-RS (60%) was the most predominant phenotype followed by PSP-P (22%). Among all of them, 42 patients were categorized into (1) intact, (2) mildly impaired, (3) moderately impaired, and (4) severely impaired cognitive groups based on Mattis-DRS-2 AMSS total scores. Variability gait domain was observed to be significantly impaired among PSP with four different cognitive categories mentioned above [Table 1 and Supplementary Table S1]. Kruskal–Wallis ANOVA revealed that more gait variability occurred in a severely impaired cognitive group as compared to the intact group (6.46 ± 4.73 versus 3.00 ± 1.04, P < 0.01). However, no significant differences were observed in any of the gait parameters between two principal PSP variants (PSP-RS versus PSP-P and PSP-RS versus PSP-non-RS).

Among all the five cognitive functions, only the impaired I/P group significantly differed from that of intact group. Unpaired t-test showed that impaired I/P had reduced velocity (P = 0.001, ES = −1.09), wider step width (P = 0.007, ES = 0.85), and more gait variability (P = 0.007, ES = 0.73) compared to having intact I/P [Figure 1]. Like gait parameters, we did not observe any significant differences in any of the cognitive functions between two principal PSP variants (PSP-RS versus PSP-P and PSP-RS versus PSP-non-RS).

Partial correlations showed significant association between different domains of gait and cognitive functions [Table 2]. Pace domain of gait was positively correlated with I/P (r = 0.42, P = 0.014). Gait variability was shown to be negatively correlated with global cognitive function (r = −0.47, P = 0.006), attention (r = −0.44, P = 0.010), initiation/perseveration (r = −0.47, P = 0.006), and conceptualization (r = −0.50, P = 0.003) as well. Postural control was also negatively correlated with I/P (r = −0.42, P = 0.016). Multivariate regression models suggested that I/P (β = 1.29, P = 0.003) was the predictor of gait velocity [R2 = 0.324, F (5, 31) = 2.97, P = 0.026] above and beyond age, disease duration, postural stability, and LEDD. Further analysis revealed that among six different components of I/P, complex verbal task (β = 2.39, P < 0.001) was the only one that can significantly predict gait velocity in PSP [F (1, 40) = 16.102, P < 0.001].

**DISCUSSION**

The present study comprehensively explores the relationship of discrete gait characteristics with various higher order cognitive process or executive functions in a large cohort of well characterized PSP patients.

**Gait variability of PSP is associated with higher order cognitive functions**

In this study, we observed that the gait variability progressively deteriorated with the increasing severity of cognitive impairment in PSP patients. In congruence with our findings, Beauchet et al.[9] found that gait variability was higher even in mild stage of Alzheimer’s disease in comparison with cognitively healthy individuals. Similarly, Hausdorff et al.[9] showed that gait variability was associated with disease severity, disease duration, and fall risk in PD. Lord et al.[7] reported a larger gait variability in older adults without apparent neurological disorders, although a similar correlation
was not evident in healthy young individuals. Hence, it is obvious that an intact cognitive function is essential for healthy walking and gait variability is altered in the early stage of cognitive impairment. We further showed that reduced function of specific cognitive domains like attention, initiation/perseveration, and conceptualization in PSP were correlated with the increasing step-to-step variability.

Dual task while walking is one of the established methods to perturb the attention domain of cognition. Due to reduced attention, PD patients displayed a greater gait variability while performing an additional task during walking. In another study, stride time variability increased from 0.04 s to 0.2 s when they were instructed to walk with a cognitive load ($P<.002$). Sheridan et al. also observed that gait variability is larger while performing more than one task simultaneously in patients with Alzheimer’s disease. All these studies reinforce our finding that attention carries a remarkable effect on gait variability. Determining a cause-effect relationship between higher order cognitive functions and gait variability is beyond the scope of this cross-sectional study.

| Gait Domains       | Selective Gait Parameters | Patients (n = 43) | Clinical Interpretation as per DRS 2 AMSS Total Scores |
|--------------------|---------------------------|-------------------|-------------------------------------------------------|
|                    |                           | Intact (n = 5)    | Mildly Impaired (n = 3) | Moderately Impaired (n = 9) | Severely Impaired (n = 25) |
| Pace               | Velocity (cm/s)           | 54.7±41.73        | 63.3±14.73             | 57.4±14.73                   | 60.5±21.28                  | 51.0±16.75                  | 0.35 |
| Rhythm             | Right swing time (s)      | 0.39±0.11         | 0.40±0.10              | 0.39±0.04                    | 0.35±0.08                   | 0.41±0.12                   | 0.37 |
| Variability        | Right step length SD (cm) | 5.28±3.96         | 3.00±1.04              | 3.15±1.01                    | 4.03±1.82                   | 6.46±1.73                   | <0.01 |
| Asymmetry          | Step time asymmetry       | 0.07±0.07         | 0.02±0.03              | 0.08±0.07                    | 0.09±0.09                   | 0.08±0.06                   | 0.18 |
| Postural control   | Right step width (cm)     | 13.38±5.74        | 11.55±4.32             | 11.02±2.90                   | 11.85±8.16                  | 14.3±5.16                   | 0.53 |

$n$, sample size. Data are presented as mean±standard deviation. The $P$ values were analyzed using one-way ANOVA test. SD, standard deviation; $P<0.01$ considered significant (indicated in bold).
The clinical significance of gait variability is quite profound. The increase in gait variability might originate from the lack of postural control. As a consequence, fall was found to be associated with a higher gait variability in various neurodegenerative conditions including PD.[13,14] Perhaps, patients of PSP with high gait variability have more risk of falls, although we have not specifically investigated this question in our current study.

**Impaired initiation/perseveration (I/P) may result in poor gait pattern**

I/P is one of the higher cognitive process which is defined as a measure of executive functional capability to initiate a task through actively translating sensory information into verbal or motor action. Walking requires mental imagination and planning to initiate and execute the motor action using multimodal activity of brain–body interaction including coordination of different components of executive function. Hence, this study result indicates that increased step width might be a compensatory phenomenon for unstable postural control in PSP patients with impaired I/P as compared to those with intact I/P.

We further propose that significant slowness of PSP gait in patients with impaired I/P could be due to following reasons. (i) A possible defense mechanism to prevent falls. (ii) Networks of motor control (like gait) and higher order cognitive functions (mainly executive functions like I/P) are believed to be interlinked. Derangement of the common anatomical substrate including dorsolateral prefrontal cortex (DLPFC)[15] may result in impairment, as observed in our study. (iii) Frontal lobe dysfunction can exhibit freezing of gait and subclinical delay in gait initiation process as observed in PD and PSP.[16]

**Semantic fluency task and gait velocity in PSP**

Our study findings reveal that complex verbal task (a semantic fluency test) of I/P predicts gait velocity in PSP. In semantic fluency test as seen in Mattis-DRS-2, participants are asked to utter as many items as possible within a stipulated period (e.g., to name grocery items within a minute). This task requires “visuo-spatial mental imagery strategy” formation through involvement of right dorsolateral prefrontal cortex (DLPFC).[17,18] DLPFC also encodes the goal or plan for movement while walking,[19] as some studies have explained that application of noninvasive brain stimulus to DLPFC significantly increases gait speed in PD.[20] Hence, we speculate that “visuospatial mental imagery strategy” might be involved in “locomotor imagery tasks,” which activates frontal regions of the brain.[21]

**Comparing gait among different psp variants**

It is well-known that PSP variants are clinically classified based on their ocular motor dysfunction, postural instability, and akinesia. Contrary to our expectation, GAITRite® failed to capture the difference in gait parameters in PSP-RS and PSP-P. Perhaps, it indicates that gait in PSP may not solely depend on the above-mentioned clinical problems, rather other factors including higher order cognitive functions may also contribute to their gait. In further support to our hypothesis, we did not observe any significant differences in any of the cognitive process among PSP variants, which was contrary to the previous finding.[22] It may reconfirm that the null result of gait differences among PSP variants was not obtained by chance. Nevertheless, the actual reasons are yet to be deciphered.

Few limitations of the present study include cross-sectional study design, which does not allow us to predict causality and a time-dependent relationship between cognitive dysfunctions and gait impairment in PSP.

Our findings emphasize the level of involvement of cognitive function particularly executive function in goal-directed motor control during walking of PSP. It shows that variability and pace are two specific gait domains, which are primarily influenced by higher order cognitive process. This may help in the decoding neuronal process of PSP patients presenting with walking difficulty, balance problems, and executive dysfunction. We suspect that DLPFC may be the area to be targeted for gait improvement in PSP patients. We showed verbal semantic fluency to be a useful predictor of walking speed in our patients. There could be some overlapping neuronal process that control both word and gait processing through mental imagery strategy formation. Through this study, we gain the experience of using DRS-2 for cognitive assessments in PSP patients and we found it useful in predicting gait abnormality in PSP patients. Assessment through I/P section of DRS-2 takes not more than 5 minutes and this method for assessing cognition is widely used in research practice. We encourage the use of this tool by clinicians as we believe that the I/P section can be associated with gait impairment in PSP patients.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Acknowledgments**

We would like to thank all the participants who have kindly taken part in the study. We would also like to acknowledge Prof Stuart Baker and Dr Mark Baker from Institute of Neuroscience, Newcastle University for their valuable comments and reviews during the process of manuscript preparation.

**Financial support and sponsorship**

This work was supported by the Institutional research fund.

**Conflicts of interest**

There are no conflicts of interest.
Chatterjee, et al.: Linking gait and cognitive functions in PSP

Annals of Indian Academy of Neurology ¦ Volume 24 ¦ Issue 6 ¦ November-December 2021

References

1. Morris R, Lord S, Bunce J, Burn D, Rochester L. Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. Neurosci Biobehav Rev 2016;64:326-45.
2. Holtzer R, Mahoney JR, Izzetoglu M, Wang C, England S, Verghese J. Online fronto-cortical control of simple and attention-demanding locomotion in humans. Neuroimage 2015;112:152-9.
3. Kim SL, Lee MJ, Lee MS. Cognitive dysfunction associated with falls in progressive supranuclear palsy. Gait Posture 2014;40:605-9.
4. Högl G, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017;32:853-64.
5. Mattis S. Dementia rating scale. Professional manual. Psychological Assessment Resources, Incorporated; 1988.
6. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martín P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 2008;23:2120-70.
7. Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent domains of gait in older adults and associated motor and nonmotor attributes: Validation of a factor analysis approach. J Gerontol A Biol Sci Med Sci 2013;68:826-32.
8. Beauchet O, Allali G, Launay C, Hermann F, Annweiler C. Gait variability at fast-pace walking speed: A biomarker of mild cognitive impairment? J Nutr Health Aging 2013;17:235-9.
9. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson’s disease. J Geriatr Psychiatry Neurol 2003;16:53-8.
10. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: The role of aging, falls, and executive function. Mov Disord 2006;21:950-7.
11. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson’s disease: Which aspects of gait are attention demanding? Eur J Neurosci 2005;22:1248-56.
12. Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: Divided attention increases gait variability in Alzheimer’s disease. J Am Geriatr Soc 2003;51:1633-7.
13. Martin KL, Blizzard L, Wood AG, Srikant H, Thomson R, Sanders LM, et al. Cognitive function, gait, and gait variability in older people: A population-based study. J Gerontol A Biol Sci Med Sci 2013;68:726-32.
14. Moe-Nilsen R, Aasland MK, Hodt-Billington C, Helbostad JL. Gait variability measures may represent different constructs. Gait Posture 2010;32:98-101.
15. Parhar R, Mahoney JR, Verghese J. Relationship of gait and cognition in the elderly. Curr Transl Geriatr Exp Gerontol Rep 2013;2:167-73.
16. Amboni M, Cozzolino A, Longo K, Picillo M, Barone P. Freezing of gait and executive functions in patients with Parkinson’s disease. Mov Disord 2008;23:395-400.
17. Biesbroek JM, van Zandvoort MJ, Kappelle LJ, Veltius BK, Biessels GJ, Postma A. Shared and distinct anatomical correlates of semantic and phonemic fluency revealed by lesion-symptom mapping in patients with ischemic stroke. Brain Struct Funct 2016;221:2123-34.
18. Szatkowska I, Grabowska A, Szymańska O. Phonological and semantic fluencies are mediated by different regions of the prefrontal cortex. Acta Neurobiol Exp 2000;60:503-8.
19. Miotto EC, Savage CR, Evans JJ, Wilson BA, Martins M, Iaki S, et al. Bilateral activation of the prefrontal cortex after strategic semantic cognitive training. Hum Brain Mapp 2006;27:288-95.
20. Torres F, Villalon E, Poblete P, Moraga-Amaro R, Linsambarth S, Riquelme R, et al. Retrospective evaluation of deep transcranial magnetic stimulation as add-on treatment for Parkinson’s disease. Front Neurol 2015;6:210.
21. Sacco K, Cauda F, Cerliani L, Mate D, Duca S, Geminiani GC. Motor imagery of walking following training in locomotor attention. The effect of ‘the tango lesson’. Neuroimage 2006;32:1441-9.
22. Picillo M, Cuoco S, Tepedino MF, Cappiello A, Volpe G, Erro R, et al. Motor, cognitive and behavioral differences in MDS PSP phenotypes. J Neurol 2019;266:1727-35.