Identifying Novel Modifiable Risk Factors in Progressive Supranuclear Palsy (PSP): A Secondary Use Analysis of Clinical Trial Data

Identifying Novel Modifiable Risk Factors in Progressive Supranuclear Palsy (PSP): A Secondary Use Analysis of Clinical Trial Data

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Abstract

Much of the current research efforts to treat neurological diseases have been focused on identifying novel disease biomarkers to aid in diagnosis, provide prognostic information, and monitor disease progression. Yet none have been found in Progressive Supranuclear Palsy (PSP). The goal of this work was to identify modifiable risk factors that predict disease progression and survival in PSP. This study performed a secondary analysis of de-identified data from several PSP clinical trials. A disease-specific rating scale, Progressive Supranuclear Palsy Rating Scale (PSPRS), and baseline variables (i.e., demographic variables, concomitant medications, baseline medical history, vital signs, etc.) were used to assess predictors of disease progression and survival. PSPRS metrics (individual items and domains) were examined and correlated with total PSPRS progression via Spearman's correlations between individual questions and domains compared to the total PSPRS. To examine predictors of PSPRS progression using baseline variables, pooled linear regression model (PLM) analyses were performed. Baseline predictors were then compared to survival (time to death) by using multivariate Cox proportional-hazards models. Eye movements (oculomotor), gait, and postures were found to be good predictors of disease progression. Within the gait, posture, and oculomotor domains, disease progression of individual items clustered together, which indicate similar underlying mechanisms. Only benzodiazepine derivatives, along with a past medical history of immune system disorders, psychiatric disorders, and renal and urinary disorders were associated with faster disease progression in PSP. Survival

analyses suggested that dysphagia, other bulbar items, and loss of oculomotor function were excellent predictors of survival in PSP patients. In summary, specific PSPRS items, PSPRS domains, concomitant medications, and baseline medical history were identified as potential risk factors that may predict progression and survival in PSP.

Dedication

This effort is dedicated to all PSP patients and their caregivers.

Acknowledgments

I am grateful to everyone I had the pleasure of working with over the course of this research project. I'd like to give my warmest thanks to my thesis director, Dr. Anne-Marie Wills, who is the Principal Investigator for this study and a leading clinician with expertise in PSP. She provided me with a platform to work on this project and invaluable advice and guidance throughout this process.

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I would also like to extend my thanks to Massachusetts General Hospital for approving this study as well as to our collaborators, Dr. Larry Golbe (CurePSP) and Dr. Adam Boxer (UCSF), for sharing their de-identified clinical trial data, without which this study would not have been possible.

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Chapter I.

Introduction

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disease that affects balance, movement, vision, speech, and swallowing. PSP is characterized by the accumulation of abnormal deposits of tau protein in nerve and glial cells in the brain.

Currently, there are no tests or techniques to definitively diagnose PSP, nor are there any proven cures or disease-modifying treatments (National Institute of Neurological Disorders and Stroke [NINDS] 2021). The major limitation of finding disease-modifying treatments is the lack of identifiable biomarkers (Stamelou & Boxer, 2015).

Much of the current neurological disease research efforts have focused on identifying novel disease biomarkers to aid in diagnosis, provide prognostic information and monitor disease progression. Yet, none have been found in PSP.

Neurodegenerative Diseases

Neurodegenerative diseases occur when nerve cells in the brain or peripheral nervous system lose function over time and ultimately die. The prevalence of neurodegenerative diseases is expected to rise with the increasing life expectancy in most countries (Global Burden of Diseases, Injuries, and Risk Factors [GBD] 2016). The most common neurodegenerative diseases are Parkinson's disease (PD) (global prevalence of over six million) and Alzheimer's disease (AD) (with 20% of women and 10% of men developing AD) (GBD, 2016; Seshadri & Wolf, 2007). Although there are some

available treatments that can relieve the physical or mental symptoms associated with these diseases, there currently are no cures and no way to slow disease progression (National Institute of Environmental Health Sciences [NIEHS] 2021).

Background on PSP

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disease that causes problems with balance, movement, vision, speech, and swallowing. PSP is characterized by the accumulation of abnormal deposits of tau protein in nerve cells in the brain. Steele, Richardson, and Olszewski described the syndrome in 1964 as an unusual constellation of supranuclear gaze palsy, progressive axial rigidity, pseudobulbar palsy, and mild dementia (Steele et al., 1964). In 1972, Steele predicted that as PSP affected different brainstem nuclei at different times and to varying degrees, clinical variants of the syndrome were likely to occur (Steel 1972). The prevalence ratio was found to be 1.39/100,000 (Golbe et al., 1988).

PSP is a progressive, disabling neurological condition that is usually fatal within 5-7 years of onset (Litvan et al., 1996). The disease burden and economic impact of PSP are also important to consider, as more research is needed to help this vulnerable population. Inuzuka et al. (2019) studied the health resource utilization of PSP in the United States and found that the total costs for PSP patients were significantly higher compared to non-PSP patients with similar characteristics, largely due to a higher number of hospitalizations, outpatient and ER visits, and prescriptions. A study in Europe found that the mean six-month economic costs of PSP were €24,491 in France, €30,643 in Germany and €25,655 in the UK, where unpaid care accounted for 68-76% (McCrone et al., 2011). Finding validated biomarkers could help discern appropriate treatments or

targeted therapies, which in turn could reduce the disease burden and economic costs of this disease.

Currently, there are no tests or techniques to definitively diagnose PSP, nor are there any proven cures or disease-modifying treatments (NINDS, 2021). The major limitation of finding disease-modifying treatments remains the lack of identifiable biomarkers (Stamelou & Boxer, 2015).

Blood-Based, Cerebrospinal Fluid (CSF), and Positron Emission Tomography (PET) Biomarkers in AD

In other neurodegenerative diseases, blood-based, cerebrospinal fluid (CSF), and positron emission tomography (PET) biomarkers have been found. In AD, identification of blood-based substances – amyloid β (Aβ) and phosphorylated tau (p-tau) – are components of the extracellular plaques and neurofibrillary tangles that are now established as core biomarkers of this disease (Zetterberg, Rohrer, & Schott, 2017). CSF Aβ42 has also been found to be one of the most well-validated biomarkers in neurodegeneration. CSF Aβ42 is reduced in patients with mild cognitive impairment (MCI) long before their progression to AD dementia and remains low throughout the disease course (Buchhave et al., 2012). Several PET ligands specific for the tau protein have been tested in PSP, however, unfortunately, these have not been shown to be able to differentiate between tau levels in the setting of AD and PSP.

Comorbidities and Survival Associations Found in Other Neurodegenerative Diseases

An association between comorbidities and survival in patients with neurodegenerative diseases may also aid in identifying biomarkers in PSP. We

hypothesized that identifying a modifiable comorbidity or concomitant medication might also lead to a treatment to improve survival from this disease.

Diabetes, Heart Disease, and Stroke as Comorbidities and Survival in Alzheimer's Disease.

Larson et al. studied the course of AD after diagnosis and investigated associations that correlate with survival in patients with AD (2004). This study found that predictors of mortality based on proportional hazards models included increased severity of cognitive impairment, history of falls, congestive heart failure, ischemic heart disease, and diabetes at baseline (Larson et al., 2004). Rajamaki et al. followed two cohorts, an AD cohort and a non-AD cohort, to determine the effect of comorbidities on survival in AD patients (2021). In both cohorts, older age, male gender, and lower socioeconomic position were associated with a worse prognosis and higher risk of death, while hip fracture, stroke, and recent cancer treatment had the most significant associations in the AD cohort only (Rajamaki et al., 2021). Therefore, we examined diabetes, heart disease, and stroke in patients with PSP.

Sleep Difficulty as a Comorbidity and Survival Association

For insomnia, Baek et al. used medical data covering the entire population of the Republic of Korea to reveal that both incidence rates and changes in the cumulative incidence of AD and vascular dementia (VaD) were greater in individuals with insomnia than in those without insomnia (2021). The researchers also found worse prognosis in patients with AD and VaD in the insomnia group in terms of higher rates of admission to long-term care facilities and higher mortality rates (Baek et al., 2021). Moreover, Arena

et al. evaluated the association between clinical symptoms and survival and found that the presence of sleep disturbances and hallucinations was associated with increased risk of death in patients with PSP (2016). Prior literature provides evidence to support that sleep difficulty, such as insomnia or other sleep disturbances, may be strongly indicative of a worse prognosis or higher mortality rate.

Anxiety and Depression as Comorbidities and Predictors of Survival

Anxiety and depression have also been shown to be strongly predictive comorbidities in other neurological diseases. For Multiple Sclerosis (MS), a chronic autoimmune inflammatory neurodegenerative disease, depression was found to be the most common psychiatric comorbidity in MS and the lifetime risk of developing depression in MS patients is greater than 50% (Mustac et al., 2021). Rasmussen et al. revealed significant associations between anxiety and frontotemporal dementia (FTD) and between depression and AD (2018). A significantly increased risk of developing FTD was observed in patients who had a history of reported anxiety, and a significantly increased risk of developing AD was observed in patients who had a history of reported depression (Rasmussen et al., 2018). Furthermore, a study with 96 patients with FTD, indicated that anxiety and suicidal ideation were correlated with a statistically significant increased mortality (Grasbeck et al., 2003). These studies provide evidence for investigating anxiety and depression as potential biomarkers for PSP progression and survival.

Medications as Risk Factors

Numerous medications have been hypothesized to be risk factors for symptoms of certain neurodegenerative disorders including MCI, dementia incidence, increased risk of falls, and short-term memory loss. For this study, an unbiased approach was used to look at all potential medication classes. Two obvious medication classes that are known in the literature to affect cognitive impairments are anticholinergic medications and benzodiazepines.

Anticholinergic Medications

First, anticholinergic medications (ACh) have been found to be associated with the incidence risk of MCI and cognitive decline among cognitively normal older adults, particularly among individuals with an elevated risk for AD (Weigand et al., 2020). These drugs block the action of acetylcholine at its receptor. Anticholinergic medications are known to cause short-term cognitive impairments, but observational studies have suggested a correlation with longer-term cognitive impairment and dementia incidence (Ancelin et al., 2006). Chuang et al. (2017) revealed long-term use of medications with mild anticholinergic activity during midlife is associated with increased risk of AD and accelerated brain atrophy. A systematic review and meta-analysis conducted to determine the relationship between anticholinergic drugs and cognitive decline found that studies with longer follow-up reported a larger cognitive decline; similarly, observational studies reported a 20% larger incidence of dementia associated with anticholinergic drug use (Pieper et al., 2020).

Benzodiazepines

Benzodiazepines have also been hypothesized to affect other neurodegenerative diseases. Benzodiazepines (BZDs) and Benzodiazepine derivatives ("Z-drugs") are medications that are widely prescribed as they have been used to reduce anxiety, prevent psychosis, and act as skeletal muscle relaxants. However, the chronic use of these medications has been hypothesized to increase the risk of falls, fractures, cognitive alterations, and the development of certain neuropathologies. For example, Kurlawala et al. aimed to determine whether chronic BZD use could cause cognitive deficits that mimic Alzheimer's disease and related conditions (2018). This case report found that a 76-year-old male did in fact exhibit an onset of short-term memory loss after a 3-year treatment with a BZD. Additionally, the elimination of the long-acting benzodiazepine drug (diazepam, in this case) led to a large improvement in the patient's cognition (Kurlawala et al., 2018). Billioti de Gage et al. conducted a study in a French population that indicated that new use of BZDs was associated with approximately a 50% increase in the risk of AD (2012). Similarly, Wu et al. concluded long-term use of BZDs might be associated with an increased risk for dementia and cognitive affectations in chronic users over a maximum follow-up of eight years. The risk of dementia was found to also be associated with a higher cumulative dosage and a longer duration of BZD exposure (Wu et al., 2009).

PSP Rating Scale (PSPRS)

The Progressive Supranuclear Palsy Rating Scale (PSPRS) is a disease-specific quantitative measure of severity in patients with PSP. PSP is a multi-faceted, multi-domain disease and the PSPRS aims to capture multiple domains of clinical impairment

in this disease (i.e., history, mentation, bulbar, ocular motor, limb motor, and gait). The PSPRS as originally developed by Golbe and Ohman-Strickland consists of 28 items with a total score ranging from 0 to 100 (Golbe & Ohman-Strickland, 2007). A higher score indicates a more severe disease progression and worse prognosis. There are six cognitive items which assess the impact of cognitive impairment on activities of daily living (ADLs). Three bulbar questions evaluate dysarthria and dysphagia, and four oculomotor questions allow the examiner to analyze saccades (voluntary upward, downward, and left and right) and eyelid function. Six gait & midline questions assess gait, stability, and neck rigidity/dystonia, and seven limb motor questions analyzes limb rigidity and dystonia, finger and toe tapping, apraxia, and tremor.

PSPRS Total Score as an Indication of Progression and Survival

The PSPRS total score has been found to be a good independent predictor of survival. Golbe and Ohman-Strickland determined that for patients with total PSPRS scores ranging from 40 to 49, three-year survival was 41.9% but four-year survival was only 17.9% (2007). The intra-class correlation coefficient for the overall scale was reported as 0.86, demonstrating good inter-rater reliability for the PSPRS total score (Golbe & Ohman-Strickland, 2007). Furthermore, another study analyzed data from a large clinical trial in PSP-Richardson's syndrome (PSP-RS) patients to analyze minimal clinically significant worsening. The minimal clinically significant worsening on the PSPRS was 5.7 points, which correlated with the mean decline over six months in the trial. This indicated that clinically meaningful change is measurable on the PSPRS over six months (Hewer et al., 2016).

Prior Clinimetric Literature on Different Domains of the PSPRS

Prior studies have attempted to analyze different domains of the PSPRS, and the published literature is detailed below.

Cognitive Domain

Cognitive impairment in PSP is most often seen in the frontal and sub-cortical functions, i.e., personality changes, difficulty in planning or carrying out day-to-day tasks, frontal and subcortical disinhibition, apathy, and emotional lability (Morris et al., 1999). The OxQUIP study assessed longitudinal changes of early cognitive symptoms in PSP by following 28 PSP participants and 28 healthy controls prospectively every three months for up to two years. At each follow-up visit, changes from baseline of the PSPRS domains were calculated. The mentation domain, which includes most of the cognitive domain items, did not show a significant change from baseline during the 18-month follow-up whereas gait & midline and ocular motor domains showed the earliest changes over time (Pereira et al., 2022).

Additionally, Ghosh et al. performed a longitudinal study over the course of one year to measure annual change in cognitive function in PSP. Despite cognition being affected in a significant number of PSP patients, the cognitive performance of the PSPRS only markedly changed in a year. In other cognition measures, such as the Frontal Assessment Battery (FAB) and the Brixton test, there was no significant change in cognition. The authors noted that several other cross-sectional studies have found no correlation between cognitive function and disease duration (Ghost et al., 2013). Overall, this notion suggests that the cognitive domain may not be a good predictor of disease progression in PSP.

Limb Motor Domain

The limb motor domain refers to limb rigidity and dystonia, finger and toe tapping, apraxia, and tremor. Hall et al. performed a clinimetric analysis of the motor section of the PSPRS and found that the factor structure suggests construct validity for the evaluation of motor signs for PSP (2015). The researchers also suggested the removal of limb dystonia, tremor, and dysphagia measures, increased internal consistency and bettered factor structure indicating that the removal of some questions may improve clinimetric features of the motor domain of the PSPRS (Hall et al., 2015).

In another study, the reliability of the PSPRS using telemedicine was assessed (Wills et al., 2022). The removal of items from the PSPRS that could not be effectively evaluated through video assessments was tested to measure the impact on measuring PSP severity and progression. Two modifications of the PSPRS were examined, one of which was the mPSPRS-25 (25 items) that removed neck rigidity, limb rigidity, and postural stability items. The results indicated that the modified mPSPRS-25 version used to administer the PSPRS remotely, significantly agreed with the original PSPRS and was highly predictive of survival (Wills et al., 2022). This finding suggests that the limb domain may not be as predictive of survival and the removal of the items may increase consistency and factor structure.

Gait & Midline Domain

The gait & midline domain assesses gait, stability, and neck rigidity and dystonia. Golbe and Ohman-Strickland applied the PSPRS for 162 patients (2007). They found that patients with scores from 40 to 49, had a likelihood of retaining some gait function of 51.7% at one year but only 6.5% at three years. Furthermore, the inter-rater reliability for

the scores of gait & midline, compared to all other domains, was found to have the highest intra-class correlation coefficient; whereas mentation and limb movement domains had the lowest correlation coefficients (Golbe & Ohman-Strickland, 2007). Arena et al. prospectively studied 35 PSP patients for assessments that occurred every six months up to two years to determine the prevalence and appearance of clinical symptoms at different stages of the disease (2016). Analyzing motor symptoms as a group, the most reported symptom at baseline occurring in 100% of the patients were motor symptoms. Slowness of movement, falls, and neck rigidity had a high prevalence from baseline, while balance and gait impairment were lower at baseline but increased in prevalence over time (Arena et al., 2016). Additionally, the OxQUIP study used the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MSD-UPDRS) Part III and the PSPRS to reliably detect motor decline less than two years after disease onset. In particular, the gait & midline PSPRS domain consistently declined over time and the earliest change was observed six months after baseline assessment (Pereira et al., 2022). Therefore, there is evidence to support that the gait & midline domain consistently proves to be a good indicator of PSP progression.

Oculomotor Domain

Ocular motor dysfunction is a core clinical feature and diagnostic criterion for PSP. Xie et al. utilized a longitudinal database of 414 patients with probable PSP-RS from 1994 to 2020. A faster progression of downgaze palsy and an older onset age were independently associated with shorter survival. Patients with survival duration within 1 year of the median survival revealed an almost linear progression of the PSPRS score and downgaze palsy score during years 2 through 6 of the disease course (Xie et al., 2022).

Although Xie et al. proposed the possibility of using the downgaze palsy progression rate to model survival in PSP, some literature on the oculomotor domain indicates otherwise. The OxQUIP study concluded that the oculomotor domain of the PSPRS, along with the gait & midline domain, showed the earliest enduring changes over time after 9 and 6 months respectively (Pereira et al., 2022). Additionally, Wills et al. examined another modification of the PSPRS, the mPSPRS-21 (21 items), for testing the reliability of the PSPRS using telemedicine (2022). The mPSPRS-21 was similar to the mPSPRS-25, with the additional removal of three ocular motor items and limb dystonia. The researchers found that the mPSPRS-21 version, also used to administer the PSPRS remotely, showed excellent agreement with the original scale and was highly predictive of survival (Wills et al., 2022). Although oculomotor abnormalities are cardinal clinical features of PSP, mixed results are found in the literature regarding their prediction of progression and survival. Additional research needs to be conducted to determine whether the oculomotor domain could have significant implications for clinical research and predicting survival.

Bulbar Domain

Bulbar palsy is caused by lesions in the upper motor neurons in the corticobulbar tract, which is characterized by dysphagia and dysarthria common to patients with PSP (Steele et al., 1964). Dysphagia has been found to be a predictor of mortality in a few neurodegenerative diseases, including PSP. Grasbeck et al. looked at predictors of mortality in FTD in 96 patients. Cox regression analyses revealed that dysphagia was significantly associated with shorter survival and increased mortality (2003). Xie et al., who examined the longitudinal database of 414 patients with probable PSP-RS from 1994

to 2020, also concluded that shorter survival was associated with a faster progression of dysphagia for liquids in PSP (Xie et al., 2022).

dell'Aquilia et al. evaluated predictors of survival in clinically diagnosed PSP patients (2013). Data on medical history, survival, and severe dysphagia were collected on forty-three outpatients' medical records and by a telephone interview to caregivers. Early dysphagia was found to be a predictor of shorter survival, and researchers have suggested considering it a possible endpoint in future PSP clinical trials (dell'Aquilia et al., 2013). Hence the bulbar domain, particularly dysphagia, has been shown to be an excellent predictor of survival in PSP and other neurodegenerative diseases.

These results suggest that some questions or domains of the PSPRS might be more predictive of PSP progression and survival than others, and it could be beneficial to identify these questions or domains and utilize them as potential quantitative biomarkers in the future.

Much of the current research efforts on neurological diseases have focused on identifying novel disease biomarkers to aid in diagnosis, provide prognostic information, and monitor disease progression. However, none have been found in PSP. The objective of this study is to identify modifiable risk factors that predict disease progression and survival in PSP to potentially aid in designing treatments or targeted therapies which can improve patient prognosis and survival.

Chapter II.

Materials and Methods

The following section details the materials and methods used throughout the course of this study. A secondary analysis was performed on data obtained from two completed clinical trials in PSP: Davunetide study (Clinical Trial of AL-108-231) and Dr. Larry Golbe's single-center database. Predictors of disease progression and survival were examined in PSP using these de-identified clinical trial data. First, means and standard deviations were calculated from individual items and domains from the PSP Rating Scale (PSPRS) across all clinical trial data. Next, the rate of change of the PSPRS was measured, and the correlation of individual items and domains with the total PSPRS progression and survival were determined. Predictors of rate of change in the total PSPRS progression were then investigated using baseline demographic and clinical variables found in the clinical trial datasets. Finally, baseline predictors of survival were examined using the Golbe dataset. All analyses were performed using R statistical software (v4.2.1; R Core Team (2021)), RStudio (RStudio Team, 2020). This study was approved by the Mass General Brigham Institutional Review Board (MGB IRB approval number: 2021P000155).

PSP Clinical Trial Datasets

All clinical trial data received were de-identified and all clinical trials were conducted with clinically probable PSP patients. Clinical trial data were requested and obtained from the following PSP studies:

- 313 participants in the Davunetide study (Clinicaltrials ID NCT01110720) (NLM, NCT01110720)
- Dr. Larry Golbe (US expert in PSP) compiled a single-center database of 490 individual patients' longitudinal PSP Rating Scale scores along with some demographic and mortality data.

Davunetide (Clinical Trial of AL-108-231)

The principal investigator, Adam Boxer, MD, PhD, along with the sponsor and collaborator, Allon Therapeutics, evaluated the safety and efficacy of AL-108-231 for the treatment of PSP. AL-108-231 is an eight amino acid peptide that fosters microtubule stability. This study was a multicenter, randomized, double-blind, placebo-controlled phase II/III trial that randomized 313 PSP-RS participants to AL-108-231 or placebo for 52 weeks. This trial produced negative results. The Davunetide dataset was provided via a data use agreement with the University of California, San Francisco (UCSF). Outcome measures from this trial included disease severity and quality of life questionnaires, concomitant medications, vital signs, medical history, and laboratory results (Clinicaltrials ID NCT01110720).

Golbe (Single-Center Database)

Dr. Larry Golbe's clinical data set was a compilation of a single-center database of patients' longitudinal PSPRS scores along with some demographic and mortality data. Dr. Golbe collected this data during routine clinical visits. A total of 490 PSP patients were included, with survival data obtained for 413 patients. The dataset was obtained via request to this author.

Written informed consent was obtained at the time of data collection and reconsent was not necessary for this secondary analysis as all the data were de-identified. The methodology utilized in this study to perform and test the aims using these datasets are outlined below.

PSPRS Analyses and their Correlation with PSP Progression

PSPRS metrics were used to assess disease progression. For the PSPRS, both individual items (28 total) and domains (7 total) were analyzed. Specifically, the domains studied were the following:

- Cognitive (sum of items 1, 2, 8,9,10, 11) [section total: 20 points]
- Bulbar [dysarthria and dysphagia] (sum of items 3, 12, 13) [section total: 12 points]
- Oculomotor [eye movements] (sum of items 14, 15, 16, 17) [section total: 16 points]
- Limb motor (sum of items 4, 18, 19, 20, 21, 22, 23) [section total: 20 points]
- Gait & midline (sum of items 5, 24, 35, 26, 27, 28) [section total: 24 points]
- Urinary incontinence (item 6 only) [section total: 4 points]

- Sleep difficulty (item 7 only) [section total: 4 points]

The mean and standard deviation for the rate of change over time (annual change) for each individual item and each domain were calculated. Spearman correlations were performed between progression rates of individual items and domains. Heat maps were produced to visualize the correlations between progression rates of individual items and domains for each dataset.

Change over time in each item and domain were examined for linearity and non-linearity. Item-to-total Spearman correlations were performed between individual items and domains and compared to the total PSPRS, to examine the relative contribution of PSPRS metrics for each dataset. Heat maps were also produced to visualize the correlations between individual items and domains for each dataset.

Predictors of Rate of Change in Total PSPRS Using Baseline Variables

The following covariates were used to analyze change from baseline over time for the total PSPRS: baseline demographic variables (age, gender, disease duration), baseline and time-varying disease severity scales including PSPRS total score, domains (cognitive, bulbar, oculomotor, limb motor, gait & midline, urination and sleep), individual items, medication use (detailed below), baseline medical history (hypothyroidism, coronary artery disease (CAD), arthritis, stroke, anxiety, depression, urinary frequency, constipation, sleep apnea), and baseline and time-varying vitals (BMI, pulse, respiratory rate, temperature), etc.

The change from baseline over time was analyzed by using the total PSPRS as a continuous variable in a pooled linear regression model with the following covariates

(listed below). Variables with Spearman's correlation coefficient ρ value < 0.2 were included in the multivariable model.:

- Baseline Demographic variables: age, age*gender, gender, disease duration
- Baseline and Time-Varying (change over the first year) Disease severity: PSPRS total score, domains including cognitive, bulbar, oculomotor, limb motor, gait & midline, urination, and sleep.
- Medication use (only medications used by greater than 10% of participants at baseline were included)
- Baseline Medical history (only those experienced by greater than 10% of participants at baseline were included)
- Baseline Vitals: BMI, pulse, respiratory rate, temperature
- Interaction terms: time *baseline PSPRS, time*age.

Baseline and Time-Varying PSPRS Metrics as Predictors of PSP Progression

For PSPRS metrics, the baseline values of individual items were compared to change over time of the PSPRS total score using the total PSPRS as a continuous variable in a pooled linear regression model, with all individual baseline item scores used as covariates. Baseline demographic variables (age, gender, and disease duration) were also included as covariates in the multivariable analyses. The PSPRS baseline variables were then assessed as potential predictors of future disease progression.

Baseline Medication Use as Predictors of PSP Progression

Medications in these datasets included the use of memantine, cholinesterase inhibitors (donepezil, rivastigmine), amantadine, anticholinergic medications (including diphenhydramine, trihexyphenidyl, antispasmodics), B vitamins (including vitamin B12, B6 and B complex vitamins), rasagiline, aspirin, ibuprofen, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), severe acute respiratory infections (SARIs), tricyclic antidepressants (TCAs), benzodiazepines, stimulants including modafinil, dopaminergic therapy (levodopa, or dopamine agonist), total daily levodopa-equivalent dose (LED), etc. Only medications used by greater than 10% of the participants at baseline were included in the analysis. After the extraction of these medication classes, each medication class was entered into a pooled linear regression model to determine potential predictors of rate of change in total PSPRS.

Baseline Medical History as Predictors of PSP Progression

Baseline medical history experienced by greater than 10% of the participants at baseline were included in the analysis. After the extraction of these medical history classes, each medical history class was then entered into a pooled linear regression model to determine potential predictors of rate of change from baseline in total PSPRS.

Baseline and Time-varying Vitals as Predictors of PSP Progression

Pooled linear regression models were created to include baseline vitals as covariates, with change over time of the PSPRS total score as the outcome variable. Baseline demographic variables (age, gender, and disease duration) were also included as

covariates in the multivariable model. Baseline and time-varying vitals were then assessed as potential predictors of disease progression.

Baseline Predictors of Survival

Baseline predictors of survival (time to death) were examined by performing survival analyses in the datasets. Survival was calculated by using multivariate Cox proportional-hazard models.

The change over the first three months and change over the first six months for each the following variables (listed below) were calculated to predict survival using multivariate Cox proportional-hazards models, to determine which of these variables predict survival better than others. Only variables which predict survival with a Spearman's correlation coefficient ρ value < 0.2 were entered into the final model:

- Baseline Demographic variables: age, gender, disease duration
- Baseline and Time-Varying Disease severity: PSPRS individual items, domains including cognitive, bulbar, oculomotor, limb motor, gait & midline, urination, and sleep.

Chapter III.

Results

The aim of this study was to determine modifiable risk factors of disease progression and survival in PSP. To do so, disease severity and quality of life questionnaires, concomitant medications, vital signs, and laboratory results were assessed as modifiable prognostic factors and predictors of disease progression.

A secondary analysis was performed on two completed multicenter clinical trials obtained from UCSF and Dr. Larry Golbe. PSP clinical trial data were successfully received from Davunetide (Clinicaltrial ID NCT01110720) and Golbe (Dr. Golbe's database).

The results from the secondary analysis performed on these datasets are described in further detail below.

Demographics

The baseline demographics of the two clinical trial datasets, Davunetide and Golbe, were calculated. The number of participants, number of participants with a disease onset over five years ago, and age (mean and standard deviation) were determined for those participants who had complete PSPRS data recorded (Table 1).

Table 1. Baseline Demographics for Davunetide and Golbe Datasets.

	Davunetide	Golbe
Participants	312	489
Mean age (SD)	67.7 (6.6)	71.5 (7.4)
Female (%)	147 (47.1%)	241 (49.3%)
Participants with disease onset over 5 years ago (%)	28 (9.5%)	119 (24.3%)

Note. This table summarizes the number of participants, age (mean and SD), gender (%), and disease duration in both Davunetide and Golbe datasets. Abbreviations: SD = standard deviation.

There were 312 and 489 participants with complete PSPRS data in the Davunetide and Golbe datasets respectively. The mean age and the number of participants with disease onset over 5 years ago were both lower in the Davunetide study than the Golbe study. This discrepancy was likely due to the nature of both studies: whereas the Davunetide study was a clinical trial (patients were enrolled at younger ages and earlier stages of the disease), the Golbe study was a collection of patient data from routine clinical visits. Gender was relatively balanced in both datasets. Wills et al. investigated different aims using both Davunetide and Golbe datasets, and their baseline demographic values were consistent with the values presented in this study (2022).

Annualized Change of PSPRS Metrics

The PSPRS is a quantitative rating scale assessing disease severity in patients with PSP. Therefore, to determine whether the change of PSPRS metrics correlated with total PSPRS progression and prediction of survival, annual change of PSPRS metrics were assessed as predictors of disease progression and survival.

PSPRS Individual Items

Annualized rate of change (mean and standard deviation) was calculated for each individual PSPRS item in both datasets. Figure 1 and Figure 2 show the annualized change of all 28 PSPRS items in the Golbe and Davunetide datasets respectively.

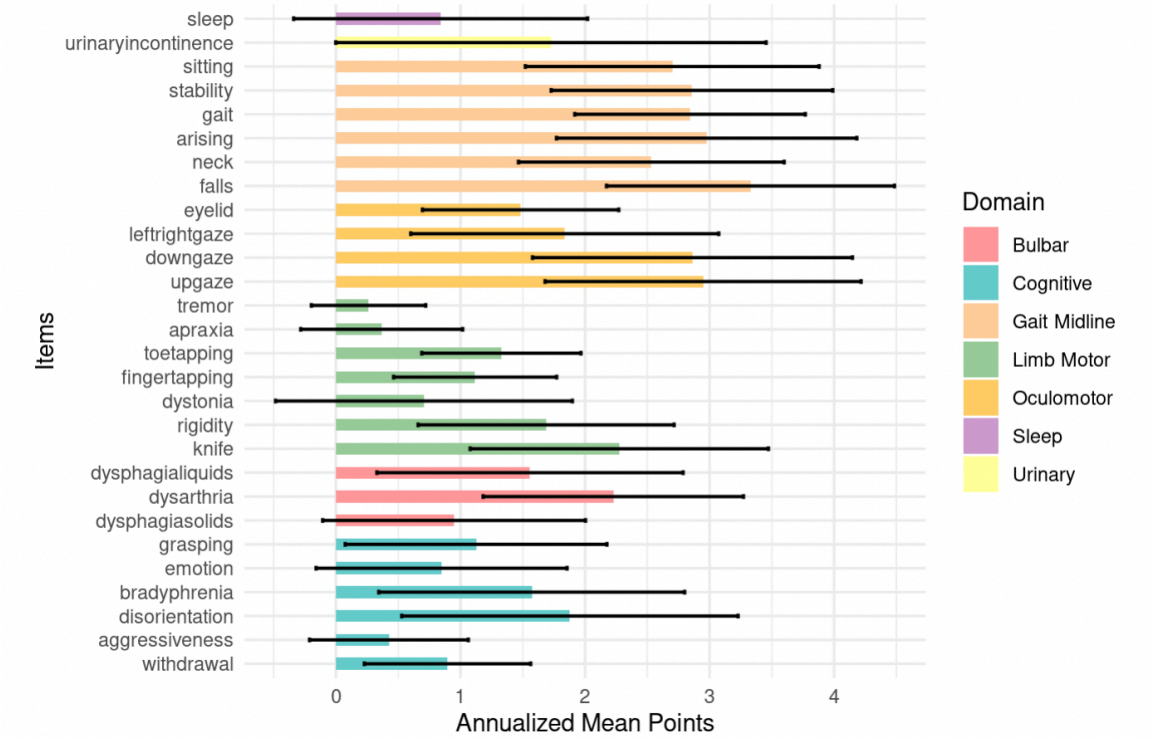

Figure 1. Annualized Change of PSPRS Items in the Golbe Dataset.

The annualized progression rates of PSPRS items in the Golbe dataset. The mean and SD rates of change for each item were plotted. The error bars indicate +/- SD. Each item in each domain were shaded a particular color as indicated by the legend above. Falls, gait, postural stability, sitting down, voluntary upward saccades, and voluntary downward saccades presented the largest rates of change in a year. All item scores increased over time. Abbreviations: stability = postural stability; sitting = sitting down; downgaze = voluntary downward saccades; upgaze = voluntary upward saccades; SD = standard deviation.

In the Golbe dataset, falls (maximum score of 4 points) had the largest rate of change per year with a mean rate of change +/- standard deviation of 3.33 +/- 1.16 points (Figure 1). Following falls, voluntary upward saccades and voluntary downward saccades (maximum scores of 4 points each) had the next highest rates of change presenting with 2.95 +/- 1.27 and 2.86 +/- 1.28 points respectively. Furthermore, gait, postural stability,

and sitting down items (maximum scores of 4 points each) also had notably large, annual rates of change. All item scores increased over time (Figure 1). For PSP participants in the Golbe study, the items in the oculomotor and gait & midline domains revealed the greatest progressions rates in a year.

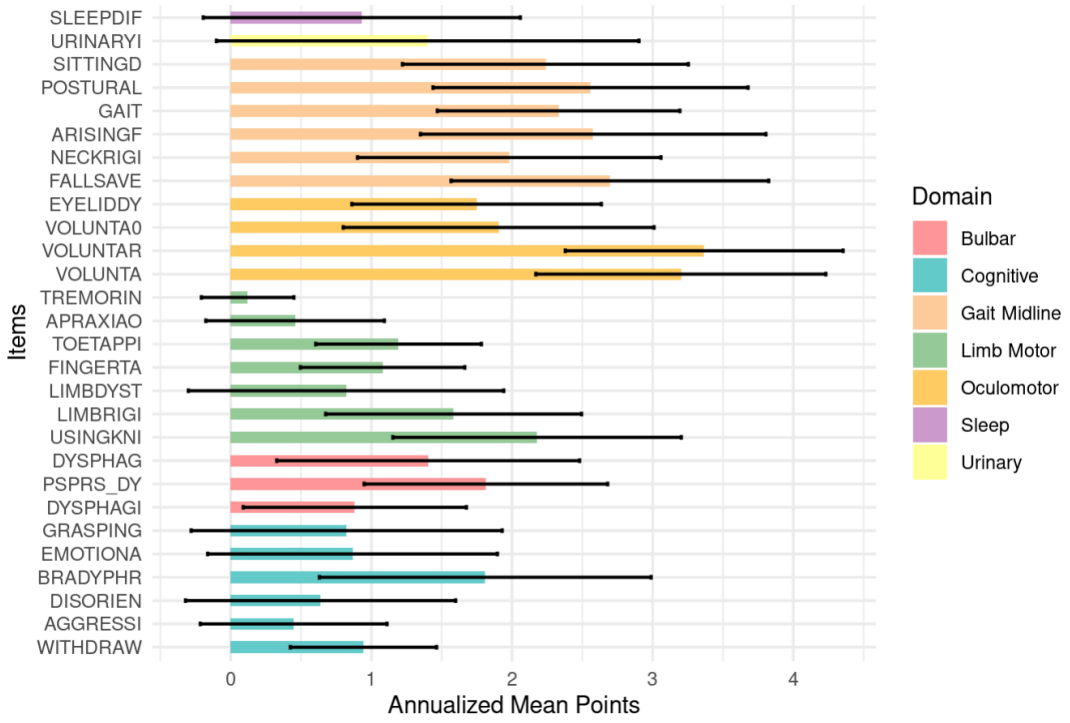

Figure 2. Annualized Change of PSPRS Items in the Davunetide Dataset.

The annualized progression rates of PSPRS items in the Davunetide dataset. The mean and SD rates of change for each item were plotted. The error bars indicate +/- SD. Each item in each domain were shaded a particular color as indicated by the legend above. Voluntary downward saccades, voluntary upward saccades, falls, arising from chair, postural stability, sitting down, and gait presented the largest rates of change in a year. All item scores increased over time. Abbreviations: voluntar = voluntary upward saccades; volunta = voluntary downward saccades; fallsave = falls; arisingf = arising from chair; postural = postural stability; sittingd = sitting down; SD = standard deviation.

In the Davunetide dataset, voluntary downward saccades and voluntary upward saccades had the largest rates of change per year with mean rates of change +/- standard deviation of 3.20 +/- 1.03 and 3.37 +/- 0.99 points (Figure 2). The Golbe dataset also revealed significantly large rates of change for both voluntary upward and downward saccades, as described above. Surprisingly, voluntary left and right saccades and eyelid dysfunction items compared to the other items in the oculomotor domain showed relatively lower annual progression rates in both datasets.

Following the oculomotor items, the next highest rates of change were seen in falls, arising from chair, and postural stability items with annual rates of 2.70 +/- 1.13, 2.58 +/- 1.23, and 2.56 +/- 1.12 points respectively. These items were followed by sitting down and gait questions which also had notably large annual rates of change. All item scores increased over time (Figure 2). Consistent with the results of the Golbe study, PSP participants in the Davunetide study also revealed that the items in the oculomotor and gait & midline domains had the largest progressions rates per year. Results of items with the greatest annual progression rates in both datasets were consistent.

PSPRS Domains

Annualized rates of change (mean and standard deviation) were calculated for each domain in both datasets: cognitive (sum of items 1, 2, 8,9,10, 11), bulbar (sum of items 3, 12, 13), oculomotor (sum of items 14, 15, 16, 17), limb motor (sum of items 4, 18, 19, 20, 21, 22, 23), gait & midline (sum of items 5, 24, 35, 26, 27, 28), urinary incontinence (item 6 only), and sleep difficulty (item 7 only). The results of the annual progression rates for each domain in Golbe and Davunetide datasets are shown in Figures 3 and 4 respectively.

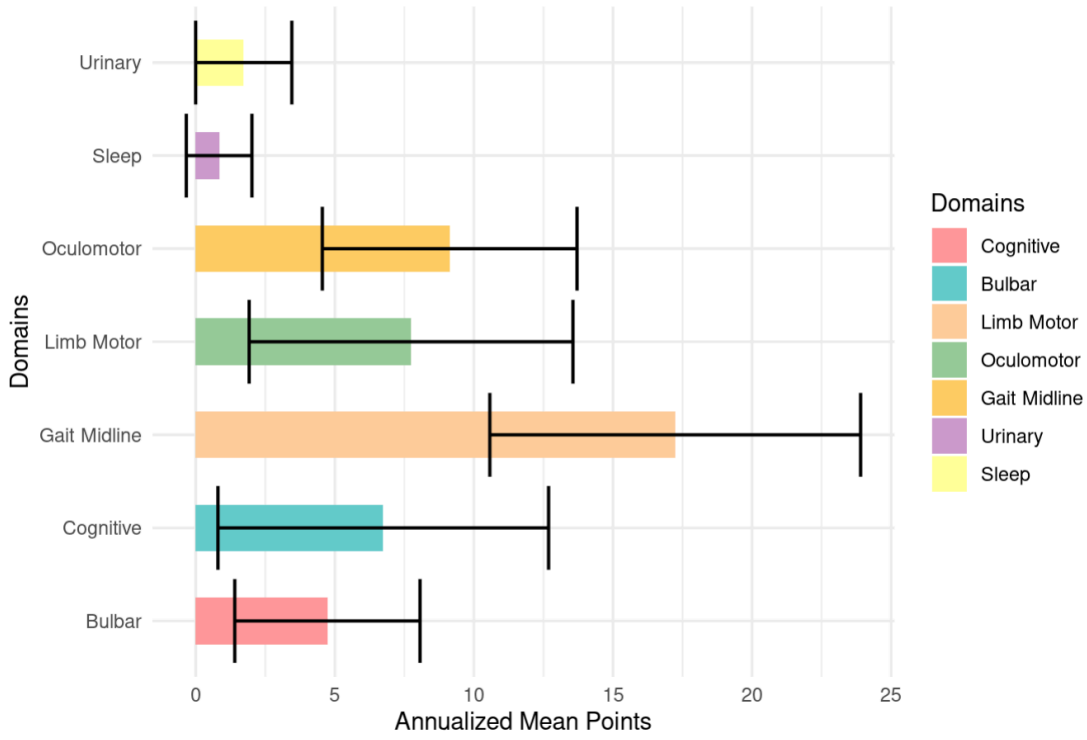

Figure 3. Annualized Change of PSPRS Domains in the Golbe Dataset.

The annualized progression rates of PSPRS domains in the Golbe dataset. The mean and SD rates of change for each domain were plotted. The error bars indicate +/- SD. Each item in each domain were shaded a particular color as indicated by the legend above. The gait & midline and oculomotor domains had the greatest annual rates of change. Abbreviations: SD = standard deviation.

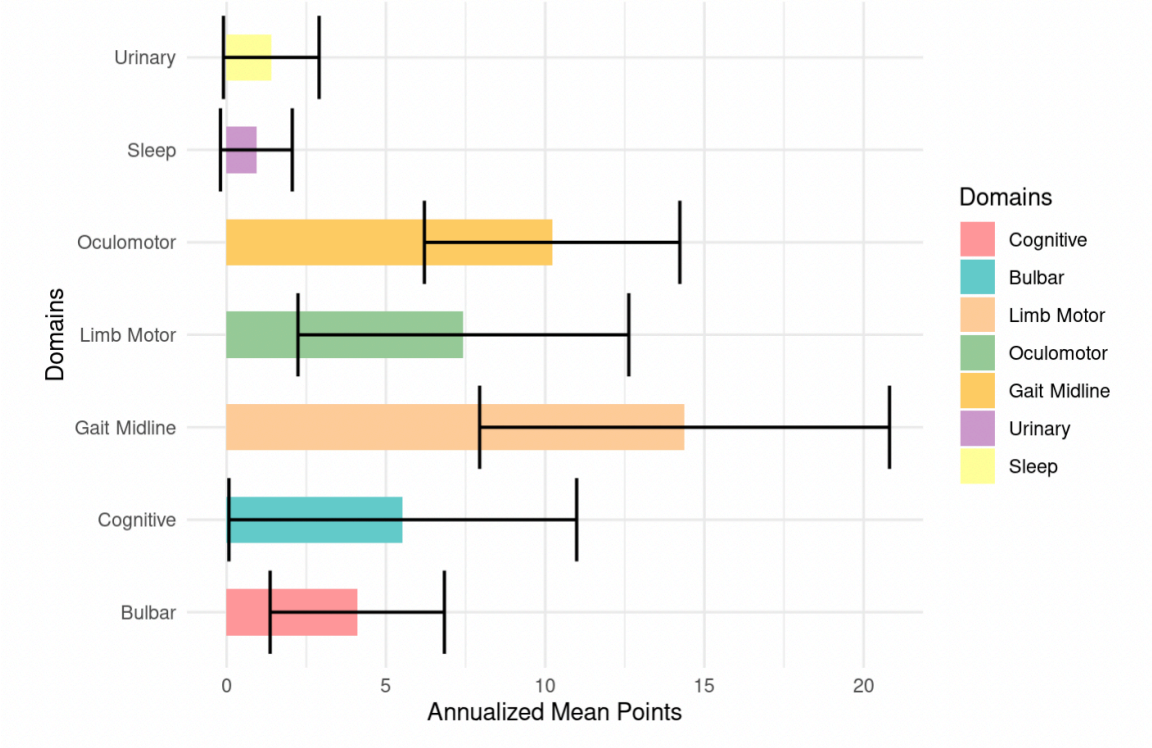

Figure 4. Annualized Change of PSPRS Domains in the Davunetide Dataset.

The annualized progression rates of PSPRS domains in the Davunetide dataset. The mean and SD rates of change for each domain were plotted. The error bars indicate +/- SD. Each item in each domain were shaded a particular color as indicated by the legend above. The gait & midline and oculomotor domains had the greatest annual rates of change. Abbreviations: SD = standard deviation.

The gait & midline domain (maximum score of 24) had the highest annual progressions rates in both datasets, with mean rates of change +/- standard deviation of 17.20 +/- 6.67 and 14.4 +/- 6.44 points in Golbe and Davunetide respectively. The oculomotor domain (maximum score of 16) had the second highest annual progression rates in both datasets with 9.13 +/- 4.58 and 10.2 +/- 4.01 points in Golbe and Davunetide respectively (Figures 3-4). This finding indicates that the gait & midline domain and the

oculomotor domain may be more useful than other domains for prediction of annualized disease progression in PSP.

Spearman Correlations of PSPRS Metrics

Spearman Correlations of Rates of Change Between Items and Domains

Spearman correlations were performed between rates of change of items versus items and domains versus domains in each dataset. Heatmaps were created for both items and domains to visualize the rates of change correlations for both Golbe and Davunetide datasets, as seen in Figures 5-8.

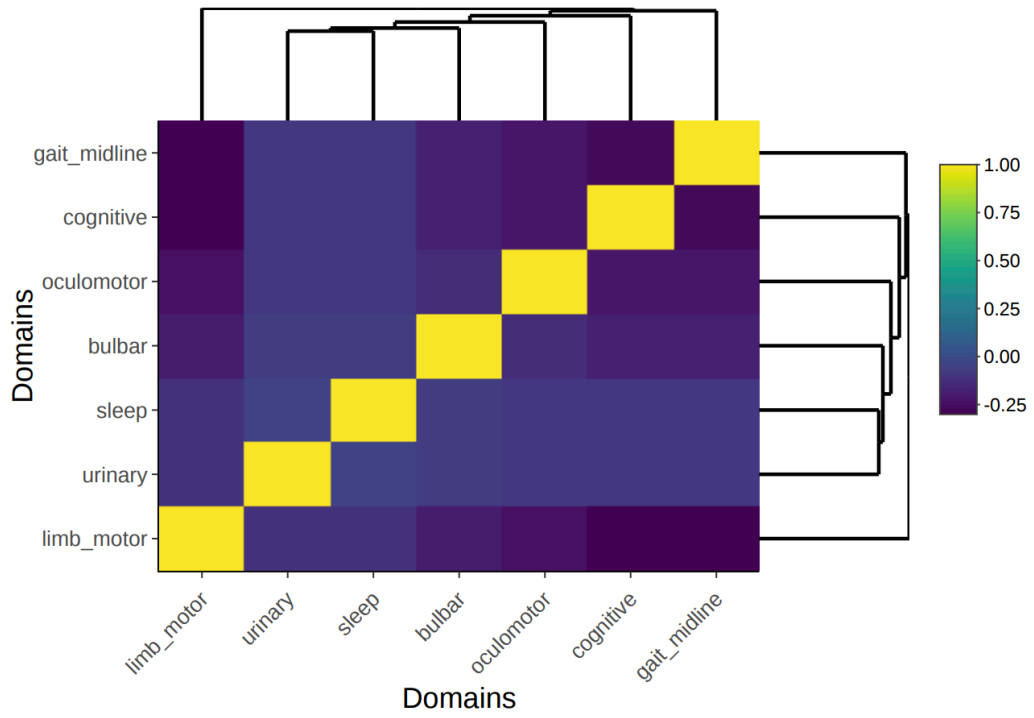

Figure 5. Heatmap of Spearman Correlations Between Rates of Change of Domains in the Golbe Dataset.

The Spearman correlations between rates of change amongst the domains in the Golbe dataset. Different ρ values were different shaded colors. Domains did not show a strong correlation with one another.

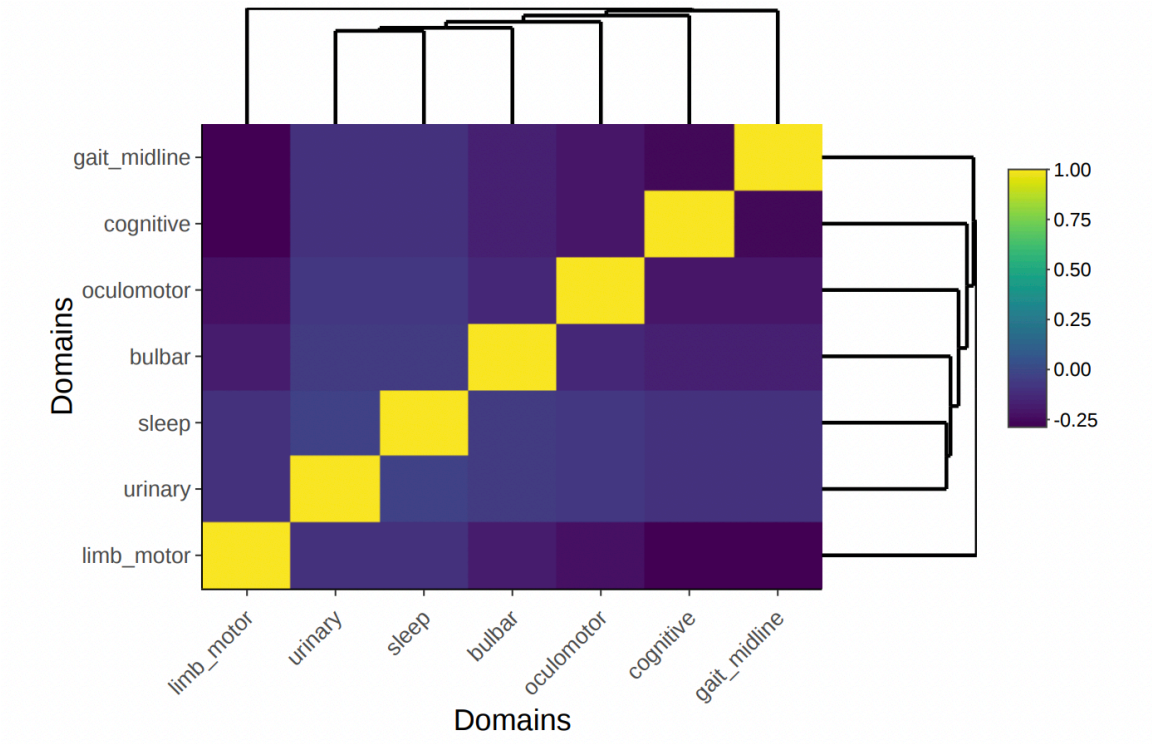

Figure 6. Heatmap of Spearman Correlations Between Rates of Change of Domains in the Davunetide Dataset.

The Spearman correlations between rates of change amongst the domains in the Davunetide dataset. Different ρ values were different shaded colors. Domains did not show a strong correlation with one another.

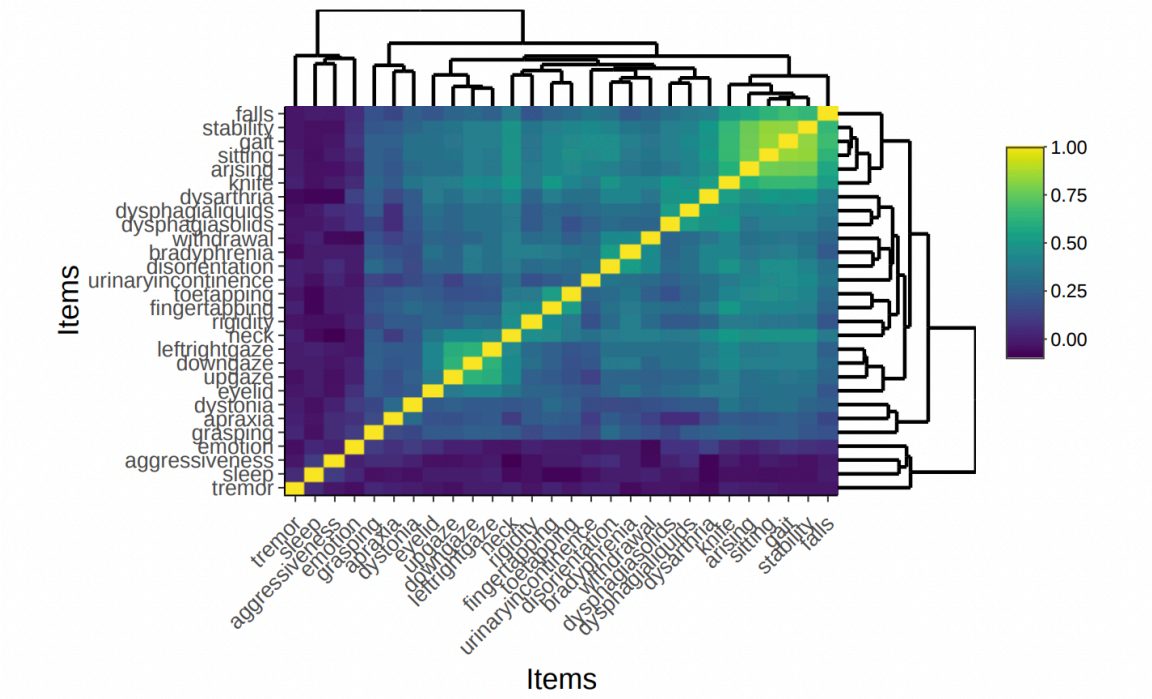

Figure 7. Heatmap of Spearman Correlations Between Rates of Change of Items in the Golbe Dataset.

The Spearman correlations between rates of change amongst the individual items in the Golbe dataset. Different ρ values were shaded different colors, denoted by the figure legend. The item-to-item rates of change visualizations show gait & midline and oculomotor clusters as indicated by the yellow shaded regions. Clustering of arising from chair, gait, postural stability, sitting down, falls, and using knife and fork, buttoning clothes, washing hands and face items were visible; and clusters of voluntary upward saccades, voluntary downward saccades, and voluntary left and right saccades were visible. Abbreviations: arising = arising from chair; stability = postural stability; sitting = sitting down; using knife and fork, buttoning clothes, washing hands and face = knife; downgaze = voluntary downward saccades; upgaze = voluntary upward saccades; leftrightgaze = voluntary left and right saccades.

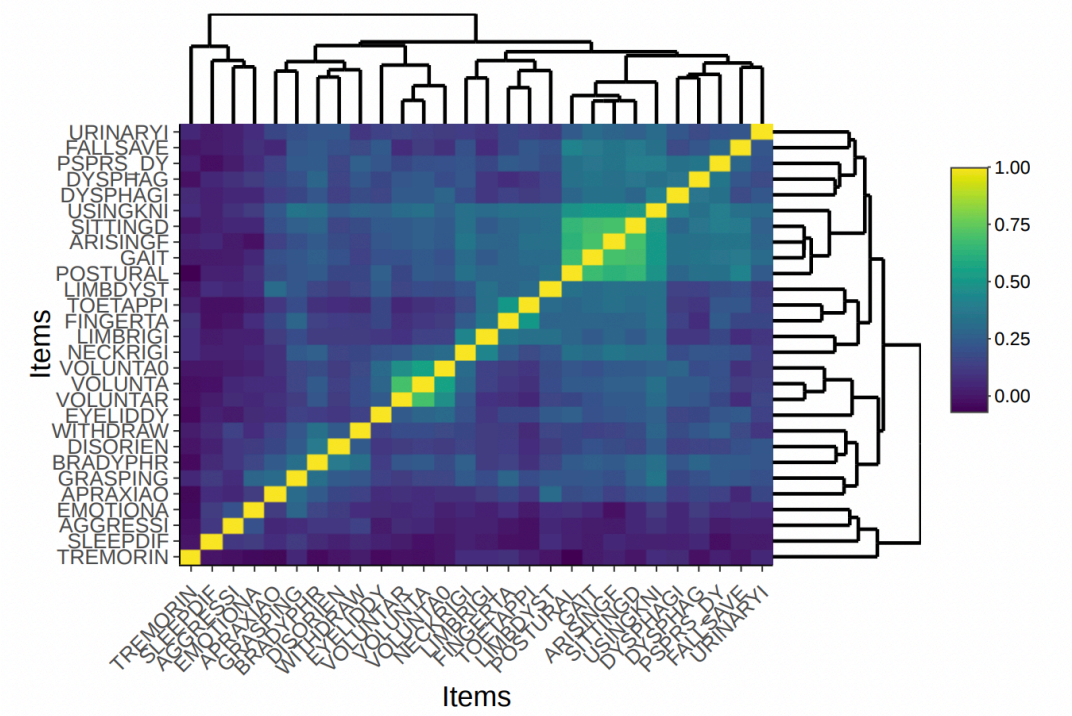

Figure 8. Heatmap of Spearman Correlations Between Rates of Change of Items in the Davunetide Dataset.

The Spearman correlations between rates of change amongst the individual items in the Davuentide dataset. Different ρ values were shaded different colors, denoted by the figure legend. The item-to-item rates of change visualizations show gait & midline and oculomotor clusters as indicated by the yellow shaded regions. Clustering of arising from chair, gait, postural stability, sitting down, and using knife and fork, buttoning clothes, washing hands and face items were visible; and clusters of voluntary upward saccades, voluntary downward saccades, and voluntary left and right saccades were visible. Abbreviations: arisingf = arising from chair; postural = postural stability; sittingd = sitting down; using knife and fork, buttoning clothes, washing hands and face = knife; voluntar = voluntary upward saccades; volunta = voluntary downward saccades; volunta0 = voluntary left and right saccades.

Rates of change between the domains did not show strong correlations with one another in either dataset, as seen by the shaded dark blue regions representing low Spearman correlation ρ values (Figures 5-6). However, in the visualizations of the rates

of change of item-to-item Spearman correlations, clustering of certain items was seen (Figures 7-8).

In the Golbe dataset, clusters of gait & midline items and oculomotor items were ascertained. Specifically, clustering of arising from chair, gait, postural stability, sitting down, and falls items were visible via the yellow shaded regions with Spearman correlation ρ values ranging from 0.6-0.8. Using knife and fork, buttoning clothes, washing hands and face item also clustered with all the gait & midline items listed above with ρ values ranging from 0.6-0.7. Additionally, another yellow-shaded cluster was visible between voluntary upward saccades, voluntary downward saccades, and voluntary left and right saccades with ρ values ranging from 0.6-0.7 (Figure 7). Therefore, cluster analysis confirmed that gait & midline and oculomotor items cluster together and the items in their respective domains likely have similar underlying mechanisms.

In the Davunetide dataset, the visualizations between the item-to-item rates of change correlations drew similar results. Yellow-shaded clusters of gait & midline and oculomotor items were also evident in the Davunetide participants. Clustering of arising from chair, gait, postural stability, and sitting down items were visible with Spearman's correlation coefficient ρ values ranging from 0.5-0.8. Using knife and fork, buttoning clothes, washing hands and face item also clustered with all the gait & midline items listed above with ρ values close to 0.5. Falls did not cluster as well with the rest of the gait & midline items. Additionally, another yellow-shaded cluster was visible between voluntary upward saccades, voluntary downward saccades, and voluntary left and right saccades with ρ values ranging from 0.5-0.7 (Figure 8). Therefore, cluster analysis again

confirmed that gait & midline and oculomotor items cluster together and the items in their respective domains likely have similar underlying mechanisms.

On the contrary, the Spearman correlations between rates of change for tremor in any part and sleep difficulty items, for instance, were very low in both datasets (these regions were shaded dark blue). This indicates that tremor and sleep may have a low likelihood to change and are poor predictors of disease progression (Figures 7-8).

Item-to-Total and Domain-to-Total PSPRS Spearman Correlations

Item-to-total and domain-to-total Spearman correlations were performed between individual questions and domains and compared to the total PSPRS, to examine the relative contribution of items and domains. The results are presented in the tables below (Tables 2-3).

Table 2. Item-to-Total PSPRS Spearman Correlations for Both Datasets.

Item	**ρ value (Golbe)**	**ρ value (Davunetide)**
withdrawal	0.507	0.366
aggressiveness	0.020	0.161
dysphagia solids	0.546	0.478
knife	0.784	0.708
falls	0.629	0.480
urinary incontinence	0.527	0.454

Item	ρ value (Golbe)	ρ value (Davunetide)
sleep	0.029	0.153
disorientation	0.613	0.388
bradyphrenia	0.573	0.509
emotion	0.104	0.241
grasping	0.396	0.486
dysarthria	0.655	0.515
dysphagia liquids	0.594	0.478
upgaze	0.558	0.473
downgaze	0.632	0.520
left right gaze	0.609	0.470
eyelid	0.508	0.418
rigidity	0.502	0.400
dystonia	0.408	0.475
finger tapping	0.544	0.414
toe tapping	0.511	0.376

Item	ρ value (Golbe)	ρ value (Davunetide)
apraxia	0.315	0.323
tremor	-0.008	0.037
neck	0.659	0.516
arising	0.756	0.688
gait	0.802	0.679
stability	0.776	0.669
sitting down	0.796	0.694

Note. This table summarizes the item-to-total Spearman correlations between items compared to the total PSPRS in both datasets. Abbreviations: ρ = Spearman's correlation coefficient; knife = using knife and fork, buttoning clothes, washing hands and face; arising = arising from chair; stability = postural stability.

Table 3. Domain-to-Total PSPRS Spearman Correlations for Both Datasets.

Domain	ρ value (Golbe)	ρ value (Davunetide)
Cognitive	-0.067	0.150
Bulbar	0.469	0.321
Limb Motor	0.368	0.305
Oculomotor	0.629	0.688

Domain	ρ value (Golbe)	ρ value (Davunetide)
Gait & Midline	0.351	0.206
Urinary	0.527	0.454
Sleep	0.029	0.153

Note. This table summarizes the domain-to-total Spearman correlations between domains compared to the total PSPRS in both datasets. Abbreviations: ρ = Spearman's correlation coefficient.

In the Golbe dataset, the highest item-to-total Spearman correlations were obtained from the following items in descending order: gait (ρ value: 0.802), sitting down (ρ value: 0.796), using knife and fork (ρ value: 0.784), postural stability (ρ value: 0.776), and arising from chair (ρ value: 0.756) (Table 2). In the Davunetide dataset, results were similar with the highest item-to-total Spearman correlations obtained from: using knife and fork (ρ value: 0.708), sitting down (ρ value: 0.694), arising from chair (ρ value: 0.688), gait (ρ value: 0.679), and postural stability (ρ value: 0.669) (Table 2). Therefore, gait & midline items (i.e., gait, sitting down, using knife and fork, postural stability, and arising from chair) appear to have the largest relative contributions to the total PSPRS score.

For the domains, both datasets suggest that the oculomotor domain provides the largest relative contribution to the total PSPRS score. In the Golbe dataset, the Spearman correlation performed between the oculomotor domain and the total PSPRS score presented with the largest ρ value compared to all other domains (ρ value: 0.629); and similarly, the Davunetide dataset supported this observation as well (ρ value: 0.688)

(Table 3). The cognitive domain appeared to have the lowest relative contribution to the total PSPRS score with ρ values of -0.067 and 0.150 in Golbe and Davunetide respectively, as expected and as is seen in the literature (Table 3).

Spearman Correlations Between Items and Domains

Spearman correlations were also performed between items versus items and domains versus domains in each dataset. Heatmaps were created for both items and domains to visualize the correlations for both Golbe and Davunetide datasets (Appendix, Figures 13-16).

These figures yielded very similar results to the heatmaps comparing rates of change between items and domains. The domains did not show any correlation with one another in either dataset, as seen by the shaded dark blue regions representing very low Spearman correlation ρ values (Figures 13-14).

Furthermore, the item-to-item Spearman correlations did show visual clustering of gait & midline and oculomotor items, consistent with the heatmaps of the rates of change of items versus items. For the Golbe dataset, clustering of arising from chair, gait, stability, and sitting down were most visible represented by dark red shaded regions with Spearman correlation ρ values ranging from 0.75-1.00. Another red cluster with slightly lower ρ values ranging between 0.60-0.75 were seen for voluntary upwards saccades, voluntary downward saccades, and voluntary left and right saccades (Figure 15). Similarly, in the Davunetide dataset, clustering of postural stability, sitting down, arising from chair, and gait items were visible with ρ values ranging between 0.60-0.80. Another red cluster was also visible between voluntary upward saccades, voluntary downward

saccades, and voluntary left and right saccades with ρ values ranging from 0.60-0.80 (Figure 16).

Interestingly, the falls item did not cluster as well with the rest of the gait & midline items in either dataset (Figures 15-16). This is likely due to the fact that falls were assessed as a historical item rather than a result of examination of participants. Frequency of falls is highly dependent on caregiver support/supervision and use of assistive devices. The cluster analysis in this study confirmed that gait & midline and oculomotor items cluster together, as was also evident in the rates of change of gait & midline and oculomotor items. This further suggests that these respective items in the gait & midline and oculomotor domains have similar underlying mechanisms.

Baseline PSPRS Metrics, Concomitant Medications, Medical History, and Labs as Predictors of Disease Progression

Baseline PSPRS Items as Predictors of Disease Progression

Baseline values of individual items were compared to change in the total PSPRS over time by using the total PSPRS scores as a continuous variable in pooled linear regression models. All PSPRS items and baseline demographics (age, gender, and disease duration) were included as covariates in the multi-variate analyses. The change from baseline of the means were plotted at different time points for each PSPRS item. No meaningful results were obtained from the PSPRS items, likely due to irregular and non-uniform visit intervals. However, a few plots of interest from the Golbe dataset were selected and shown below (Figure 9).

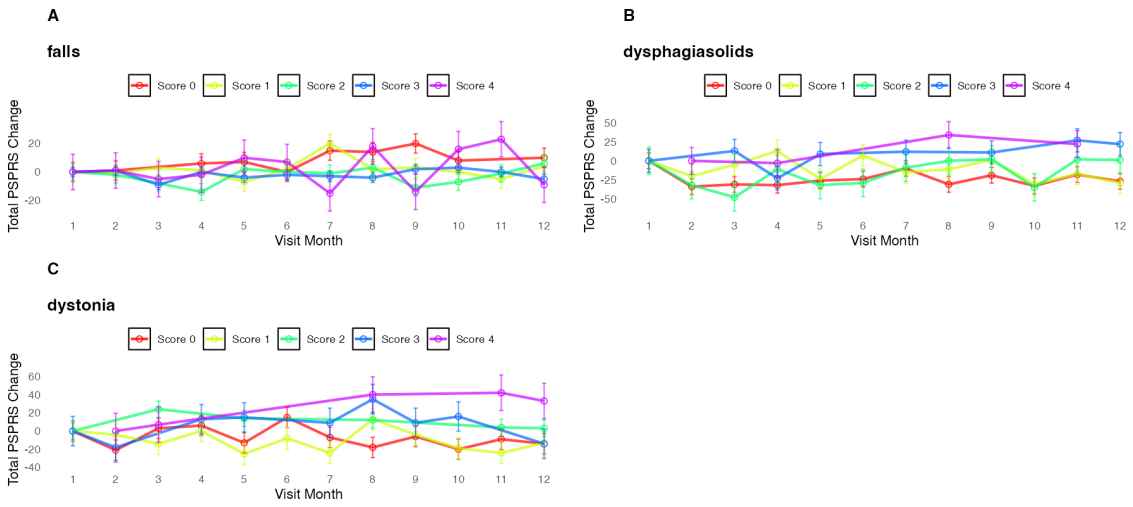

Figure 9. Change in Total PSPRS Scores from Baseline Plotted over Time for Three Items.

The change in total PSPRS scores from baseline were plotted over time for (A) falls, (B) dysphagia for solids, and (C) dystonia items in the Golbe dataset. The different baseline scores (scores 0-4) were plotted as separate groups to see their rates of progression over time. The error bars indicate +/- SD. Abbreviations: SD = standard deviation.

Falls did not show good separation for the different groups (baseline scores 0-4), which again suggests that this item may not be properly captured and assessed in the PSP rating scale (Figure 9A). Dysphagia for solids, however, does show good separation as patients with worse dysphagia for solids at baseline (higher scores) progressed faster than those with lower scores of dysphagia (Figure 9B). The dystonia item revealed similar results; the more advanced the patient's dystonia was at baseline (the higher the score), the faster the rate of progression (Figure 9C).

Baseline Concomitant Medications as Predictors of Disease Progression

Data on baseline medication use were only available in the Davunetide dataset, therefore, all medication analyses were performed using the Davunetide study data. Medications used by greater than 10% of the participants at baseline were extracted. These medication classes were entered into a pooled linear regression model and were assessed as potential predictors of disease progression.

The Bonferroni correction was utilized to decrease type I error due to multiple testing across the models. Thus, only highly significant (***) medications were considered truly significant in the multivariate analyses, where *** indicated a p-value < 0.001. The multivariate pooled linear regression model results revealed only one significant (***) medication class: benzodiazepine derivatives (p-value = 2.786×10^{-4}). Gender and disease duration were also significant in the multivariate analysis (Table 4).

Table 4. Pooled Regression Model Results for the Interaction between Change in PSPRS and Time for Participants on Each Medication Class.

Medication Class	**Estimate**	**Std. Error**	**t-value**	**Pr(>|t|)**
Other Therapeutic Products	2.970	2.533	1.172	0.241
Other Lipid Modifying Agents	1.266	2.316	0.547	0.585
Platelet Aggregation Inhibitors	0.237	2.106	0.113	0.910

Medication Class	Estimate	Std. Error	t-value	Pr(>|t|)
Beta Blocking Agents, Selective	-1.494	2.542	-0.588	0.557
Various Alimentary Tract and Metabolism Products	-1.959	2.467	-0.794	0.427
Vitamin D and Analogues	-2.150	2.492	-0.863	0.388
Propionic Acid Derivatives	-5.853	2.881	-2.032	0.042 *
Ace Inhibitors, Plain	-0.791	2.204	-0.359	0.720
Other Opthalmologicals	-8.121	4.017	-2.022	0.043 *
Dihydropyridine Derivatives	3.313	2.749	1.205	0.228
Angiotensin II Antagonists, Plain	0.539	2.895	0.186	0.852
Dopa and Dopa Derivatives	1.878	2.0741	0.905	0.366
Adamantane Derivatives	2.791	2.300	1.213	0.225

Medication Class	Estimate	Std. Error	t-value	Pr(>|t|)
Other Antidepressants	1.293	2.397	0.539	0.590
Benzodiazepine Derivatives	14.475	3.973	3.643	2.786×10^{-4} ***
Selective Serotonin Reuptake Inhibitors	5.193	2.209	2.351	0.019 *
Thyroid Hormones	3.301	2.420	1.364	0.173
HMG-CoA Reductase Inhibitors	1.526	2.175	0.702	0.481
Urinary Antispasmodics	7.791	2.887	2.699	0.007 **
Osmotically Acting Laxatives	-0.384	3.372	-0.114	0.910
Proton Pump Inhibitors	4.960	2.695	1.841	0.066
Multivitamins, Plain	2.674	2.749	0.973	0.331
Anilides (Acetaminophen)	1.252	2.472	0.507	0.613

Medication Class	Estimate	Std. Error	t-value	Pr(>|t|)
Vitamin B12 (Cyanocobalamin and Analogues)	0.446	2.511	0.177	0.859
Natural Opium Alkaloids	-3.720	5.287	-0.704	0.482
Glucocorticoids	-14.100	8.787	-1.605	0.109
Benzodiazepine Related Drugs	-4.775	3.421	-1.396	0.163

*Note. This table summarizes the pooled regression model results for the interaction between change in PSPRS and time for participants taking each medication class. Only medication classes used by at least 10% of the study population at baseline were included in the analysis. Abbreviations: Std. Error = standard error; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

For the benzodiazepine derivatives medication class, a contrast of interest graph was plotted for both groups (participants on medication versus not on medication) over time. The change from baseline of the PSPRS total scores were plotted at different time points to compare the progression of the PSPRS over time in both groups. This graph is shown in Figure 10.

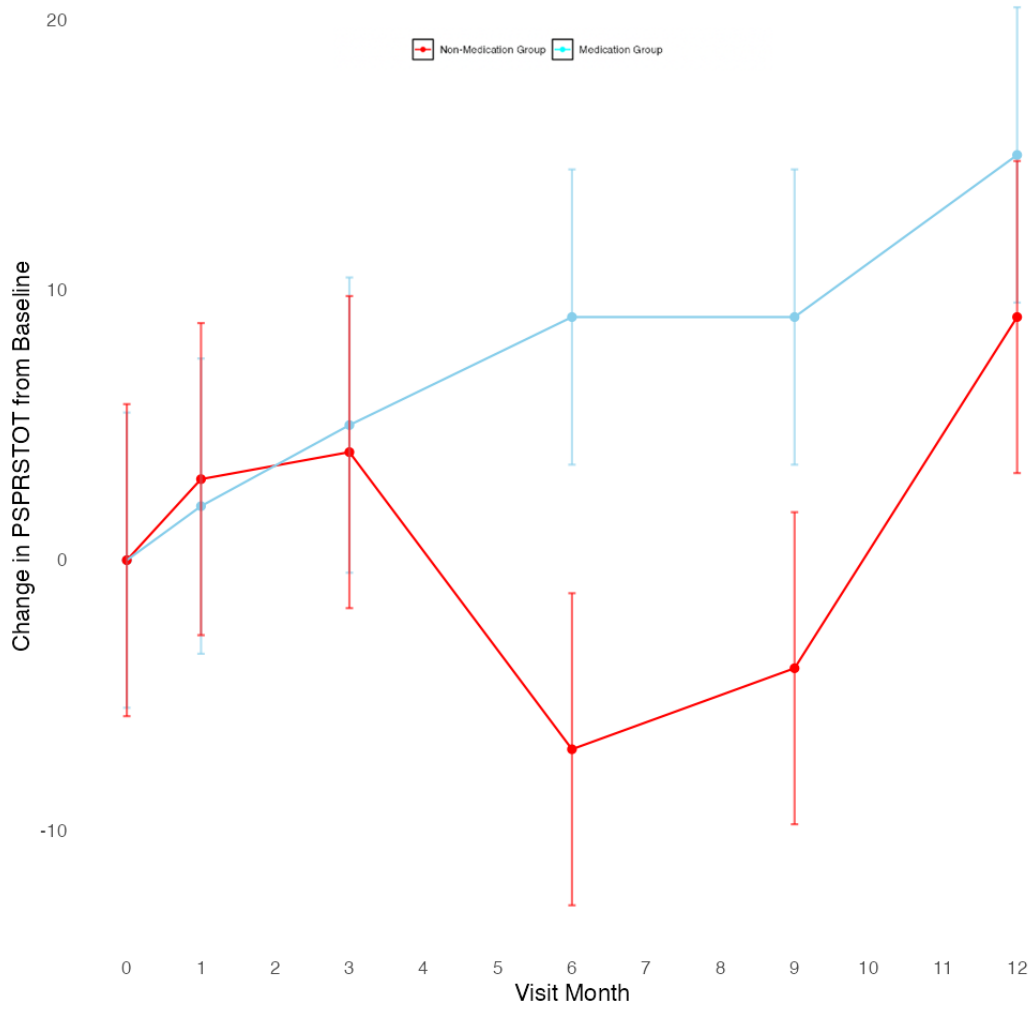

Figure 10. Contrast of Interest Graph Plotting Change in Total PSPRS from Baseline over Time for Benzodiazepine Derivatives.

The change in total PSPRS scores were plotted from baseline over time for benzodiazepine derivatives. Participants on medication at baseline (medication group) and participants not on medication at baseline (non-medication group) were plotted to compare their rates of progression over time. The error bars indicate +/- SD. Abbreviations: SD = standard deviation.

Benzodiazepine derivatives presented large differences between participants in the medication group (blue) and non-medication group (red). Participants on

benzodiazepine derivatives at baseline progressed faster than those not on these medications, indicating that patients taking benzodiazepine derivatives may correlate with worsening disease progression in PSP (Figure 10).

The raw Davunetide data for concomitant medications showed the following: the benzodiazepine derivatives class included medications such as lorazepam, temazepam, alprazolam, midazolam, clonazepam, diazepam, tetrazepam, bromazepam, and oxazepam which were taken for indications of anxiety and insomnia. This result suggests that these medications should be prescribed with caution to prevent worsening of the disease in patients with PSP.

Baseline Medical History as Predictors of Disease Progression

Data on baseline medical history were only available in the Davunetide dataset, therefore, all medical history analyses were performed using the Davunetide study data. Baseline medical history experienced by greater than 10% of the participants at baseline were extracted. These medical history classes were entered into a pooled linear regression model by using the total PSPRS scores as a continuous variable and were assessed as potential predictors of disease progression.

The Bonferroni correction was again used to decrease type I error due to multiple testing across the models. Thus, only highly significant (***) baseline medical history classes were considered truly significant in the multivariate analyses, where *** indicated a p-value < 0.001. The multivariate pooled linear regression model results indicated that the following medical history classes were significant (***): infections and infestations (p-value = 1.883×10^{-4}), immune system disorders (p-value = 2.198×10^{-6}), renal and urinary disorders (p-value = 2.449×10^{-9}), and psychiatric disorders (p-value = $1.455 \times$

10^{-10}). Gender, age, and disease duration were also significant in the multivariate analyses (Table 5).

Table 5. Pooled Regression Model Results for the Interaction between Change in PSPRS and Time for Participants Experiencing Each Medical History Class.

Baseline Medical History Class	**Estimate**	**Std. Error**	**t-value**	**Pr(>|t|)**
Eye Disorders	1.415	0.503	2.813	0.005 **
Gastrointestinal Disorders	1.109	0.424	2.617	0.009 **
Immune System Disorders	3.151	0.665	4.736	2.198×10^{-6} ***
Musculoskeletal and Connective Tissue Disorders	-1.150	0.390	-2.947	0.003 **
Nervous System Disorders	0.418	0.325	1.288	0.198
Reproductive System and Breast Disorders	0.414	0.615	0.674	0.500
Surgical and Medical Procedures	0.416	0.353	1.180	0.238
Vascular Disorders	0.514	0.435	1.184	0.237

Baseline Medical History Class	**Estimate**	**Std. Error**	**t-value**	**Pr(>|t|)**
Infections and Infestations	-2.490	0.667	-3.735	1.883×10^{-4} ***
Psychiatric Disorders	2.482	0.387	6.414	1.455×10^{-10} ***
Renal and Urinary Disorders	2.944	0.493	5.968	2.449×10^{-9} ***
Endocrine Disorders	1.029	0.757	1.361	0.174
Metabolism and Nutrition Disorders	0.692	0.426	1.624	0.104
Cardiac Disorders	1.266	0.642	1.972	0.049 *
General Disorders and Administration Site Conditions	1.078	0.903	1.194	0.233
Skin and Subcutaneous Tissue Disorders	2.529	0.781	3.237	0.001 **
Investigations	1.462	0.682	2.146	0.032 *

Note. This table summarizes the pooled regression model results for the interaction between change in PSPRS and time for participants experiencing each medical history class. Only medical history classes experienced by at least 10% of the study population at

*baseline were included in the analysis. Abbreviations: Std. Error = standard error; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

For each significant medical history class, a contrast of interest graph (participants with medical history versus no medical history) were plotted for both groups over time. The change from baseline of the means were plotted at different time points to compare the progression of the PSPRS over time in both groups. The graphs of the listed medication classes are shown in Figure 11.

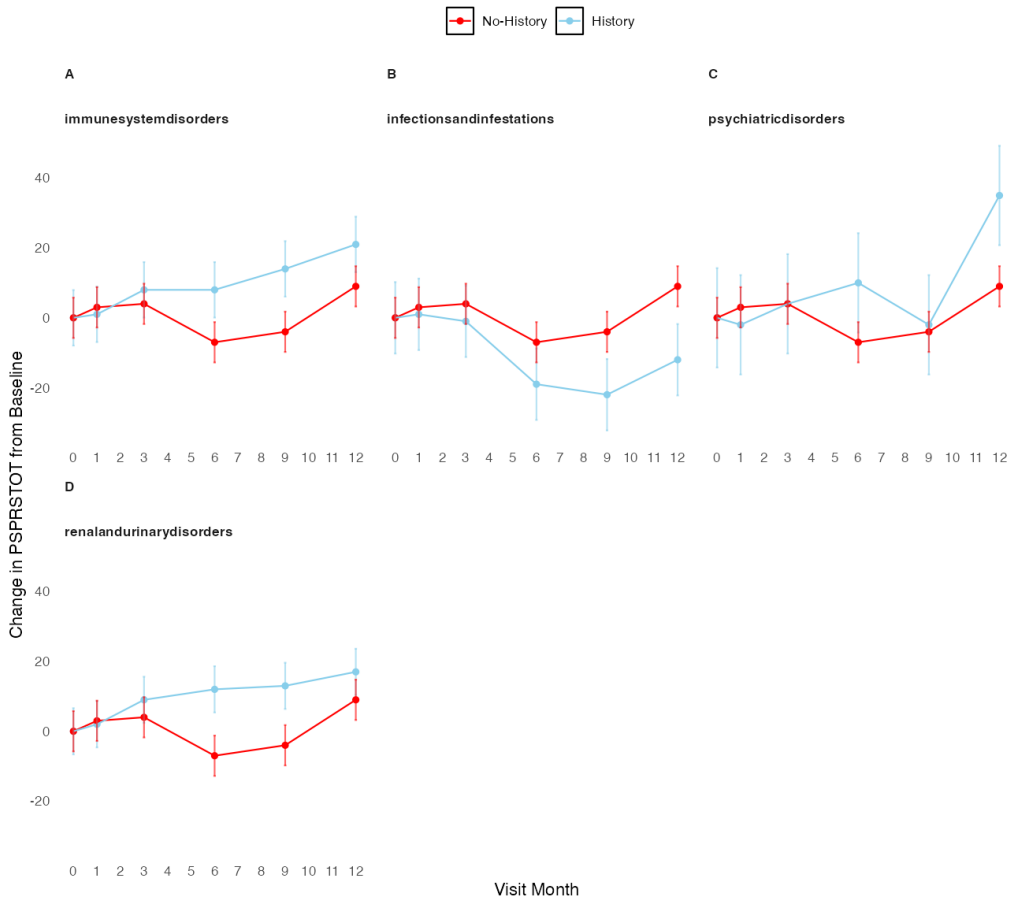

Figure 11. Contrast of Interest Graphs Plotting Change in Total PSPRS from Baseline over Time for Four Baseline Medical History Classes.

The change in total PSPRS scores were plotted from baseline over time for (A) immune system disorders, (B) infections and infestations, (C) psychiatric disorders, and (D) renal and urinary disorders. Participants experiencing an indication in a medical history class at baseline (history group) and participants not experiencing the indication at baseline (no-history group) were plotted to compare their rates of progression over time. The error bars indicate +/- SD. Abbreviations: SD = standard deviation.

Immune system disorders (i.e., allergies and drug hypersensitivity) presented significant differences between participants who had a history of indications in this class at baseline (blue) and no history at baseline (red). Participants who had a history of immune system disorders progressed faster than those with no history, indicating that medical history of this class may worsen PSP disease progression (Figure 11A). Moreover, a medical history of psychiatric disorders (i.e., depression, insomnia, anxiety, affect lability, and personality change) and renal and urinary disorders (i.e., urinary incontinence, micturition urgency, pollakiuria, and nephrolithiasis) showed similar results with large differences in the rates of progression between participants with a history of these classes and participants with no history (Figure 11C, Figure 11D). These trends suggest that psychiatric and renal and urinary disorders may also significantly correlate with a PSP-worsening effect.

However, a medical history of infections and infestations presented a rather strange result. The most common infections and infestations in the raw Davunetide dataset included indications of rhinitis, sinusitis, UTIs, appendicitis, cystitis, and herpes zoster. The contrast of interest graph for infections and infestations revealed that

participants with a history of this class progressed slower than those with no history (Figure 11B). This was a paradoxical finding and was not expected.

Therefore, apart from the infections and infestation class, these results suggest that immune system disorders, psychiatric disorders, and renal and urinary disorders may likely be associated with faster disease progression. Movement disorder specialists should be cognizant of these classes in patients with or at risk of PSP.

Vital Signs as Predictors of Disease Progression

Vitals data were only included in the Davunetide dataset, therefore, all analyses on the vital signs were performed using the Davunetide study data. Pooled linear regression models were created to include baseline vitals as covariates, with change over time of the PSPRS total score as the outcome variable. Baseline demographic variables (age, gender, and disease duration) were also included in the multivariable analysis. Baseline and time-varying vitals were then assessed as potential predictors of disease. No meaningful results were obtained from the analyses of the vital signs. However, a graph of each of the vitals' change over time from baseline were plotted below (Figure 12).

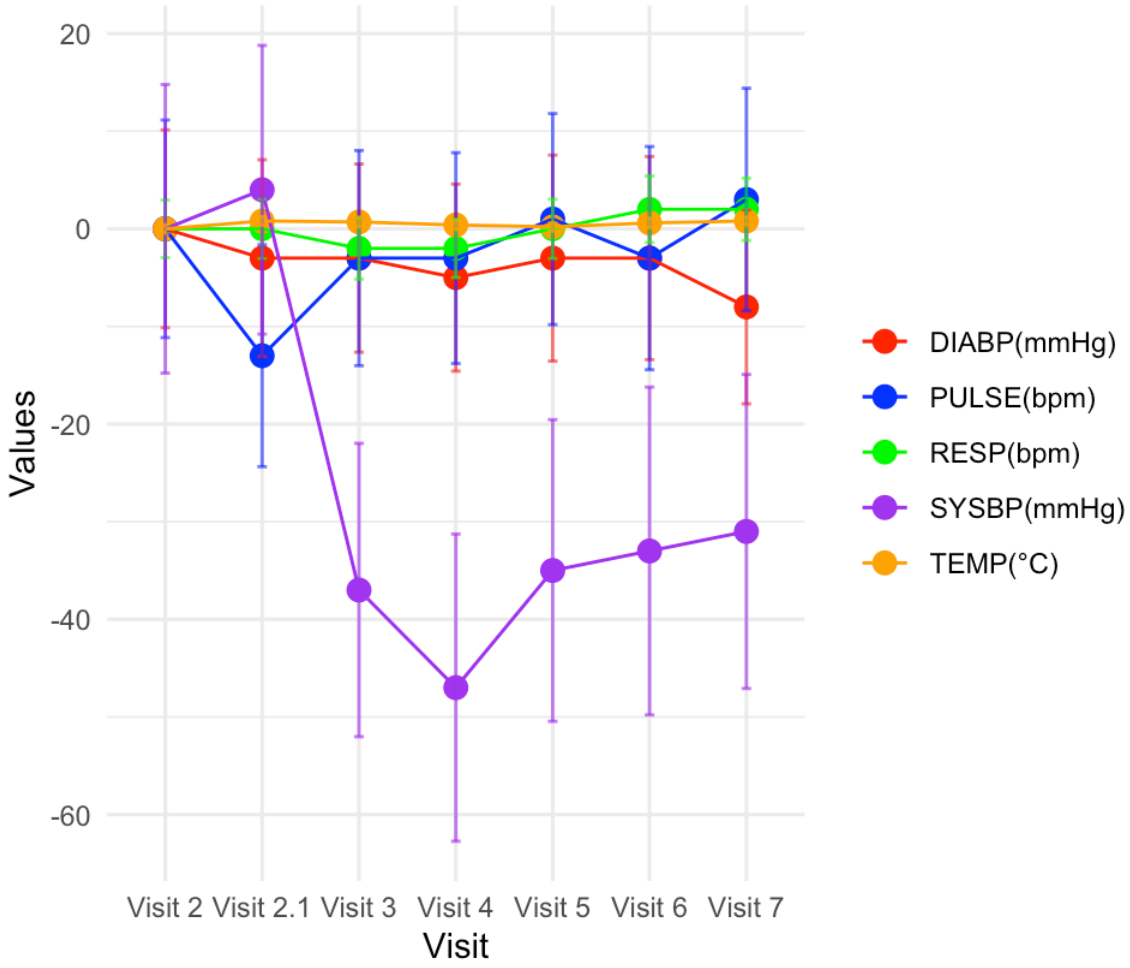

Figure 12. Illustration of Change over Time for all Vitals from Baseline.

The change over time from baseline are shown in this graph for all vital signs. Systolic blood pressure (SYSBP) drastically decreased from baseline over time. The error bars indicate +/- SD. Abbreviations: DIABP = diastolic blood pressure; PULSE = pulse rate; RESP = respiratory rate; SYSBP = systolic blood pressure; TEMP = temperature; SD = standard deviation.

Systolic blood pressure (SYSBP) drastically decreased from baseline over time, while all other vital signs stayed relatively constant over the course of a year (Figure 12). This drastic change in systolic blood pressure could be due to orthostatic hypotension (OH), a symptom that is common in neurodegenerative disorders, which is when systolic

blood pressure rapidly drops when a person stands up from a seated or lying position (Sorbera et al., 2019). However, this hypothesis was unable to be tested as the raw Davunetide vital signs dataset did not distinguish how the measurements were taken and whether the vitals were measured when patients were sitting, standing, or lying down.

Survival Analyses - Cox Proportional-Hazards Model

As the Davunetide study did not include survival data for all participants, only the Golbe dataset was used for assessing predictors of survival. Because the Golbe dataset only included basic demographics, PSPRS metrics, and time of death, the analysis was limited to PSPRS metrics (items and domains) and their association with survival.

PSPRS Metrics as Predictors of Survival

Change over the first three months and change over the first six months in each item and domain were analyzed to predict survival using multivariate Cox proportional-hazards models, to determine change in which questions and domains would predict survival. Age, gender, and disease duration were also included in the multivariate models. Forward and backward selection models were performed to see which items and domains remained significant (backward selection models are included in the Appendix).

The Bonferroni correction was again utilized to decrease type I error due to multiple testing across the models. Thus, only items and domains that were highly significant (***) were considered truly significant in the multivariate analyses, where *** indicated a p-value < 0.001. The results of the forward selection model survival analyses are shown in Tables 6-9 and the results of the backward selection model survival analyses are shown in Tables 10-13.

Table 6. Multivariate Cox Proportional-Hazards Model (Forward Selection Model) for all PSPRS Items to Predict Survival using Disease Progression after the First Three-Months.

Item	HR (95% CI)	P values
withdrawal	2.342 (1.976, 2.895)	0.155
aggressiveness	2.944 (2.446, 3.680)	0.424
dysphagia solids	3.285 (2.799, 3.953)	0.019 *
knife	3.314 (2.774, 4.084)	0.027 *
falls	2.668 (2.333, 3.116)	0.800
urinary incontinence	2.686 (2.493, 2.912)	0.765
sleep	2.904 (2.643, 3.220)	0.175
disorientation	2.650 (2.384, 2.984)	0.660
bradyphrenia	2.979 (2.604, 3.473)	0.192
emotion	2.649 (2.370, 3.003)	0.672
grasping	3.059 (2.684, 3.546)	0.079
dysarthria	2.987 (2.541, 3.610)	0.269
dysphagia liquids	3.385 (2.929, 3.988)	0.002 **
upgaze	2.333 (2.083, 2.660)	0.024 *

Item	HR (95% CI)	P values
downgaze	3.118 (2.657, 3.756)	0.097
left right gaze	2.882 (2.538, 3.330)	0.383
eyelid	3.378 (2.772, 4.277)	0.030 *
rigidity	3.226 (2.813, 3.766)	0.013 *
dystonia	2.501 (2.257, 2.806)	0.149
finger tapping	2.579 (2.133, 3.270)	0.635
toe tapping	2.498 (2.100, 3.094)	0.410
apraxia	2.700 (2.261, 3.349)	0.945
tremor	3.173 (2.422, 4.514)	0.290
neck	2.943 (2.517, 3.534)	0.338
arising	2.569 (2.246, 3.006)	0.460
gait	3.304 (2.467, 4.863)	0.212
stability	2.307 (1.945, 2.861)	0.125
sitting down	3.611 (2.903, 4.695)	0.008 **
age at baseline	2.727 (2.677, 2.778)	0.743

Item	HR (95% CI)	P values
duration of disease	2.518 (2.401, 2.647)	0.003 **
sex (male)	3.000 (2.345, 4.121)	0.468

*Note. Multivariate Cox proportional-hazards model (forward selection model) results for all items to predict survival using disease progression after the first three-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; knife = using knife and fork, buttoning clothes, washing hands and face; arising = arising from chair; stability = postural stability; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Table 7. Multivariate Cox Proportional-Hazards Model (Forward Selection Model) for all PSPRS Domains to Predict Survival using Disease Progression after the First Three-Months.

Domain	HR (95% CI)	P values
Cognitive	2.771 (2.658, 2.893)	0.369
Bulbar	3.166 (2.991, 3.362)	4.080×10^{-8} ***
Limb Motor	2.790 (2.671, 2.919)	0.245
Oculomotor	2.851 (2.740, 2.970)	0.018 *
Gait & Midline	2.799 (2.701, 2.903)	0.108
Urinary	2.809 (2.610, 3.039)	0.391
Sleep	2.855 (2.619, 3.137)	0.275

Domain	HR (95% CI)	P values
Age at Baseline	2.738 (2.693, 2.784)	0.390
Duration of Disease	2.511 (2.404, 2.629)	8.660×10^{-4} ***
Sex (Male)	3.279 (2.580, 4.428)	0.135

*Note. Multivariate Cox proportional-hazards model (forward selection model) results for all domains to predict survival using disease progression after the first three-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Table 8. Multivariate Cox Proportional-Hazards Model (Forward Selection Model) for all PSPRS Items to Predict Survival using Disease Progression after the First Six-Months.

Item	HR (95% CI)	P values
withdrawal	2.545 (2.251, 2.932)	0.344
aggressiveness	2.993 (2.635, 3.457)	0.145
dysphagia solids	3.279 (2.955, 3.676)	2.394×10^{-4} ***
knife	2.792 (2.523, 3.125)	0.617
falls	2.679 (2.443, 2.965)	0.769
urinary incontinence	2.799 (2.656, 2.959)	0.279
sleep	2.884 (2.696, 3.100)	0.087

Item	HR (95% CI)	P values
disorientation	2.551 (2.383, 2.745)	0.088
bradyphrenia	2.828 (2.604, 3.092)	0.359
emotion	2.565 (2.387, 2.773)	0.141
grasping	3.093 (2.829, 3.408)	0.004 **
dysarthria	2.976 (2.664, 3.367)	0.113
dysphagia liquids	3.149 (2.871, 3.482)	0.001 **
upgaze	2.461 (2.284, 2.670)	0.018 *
downgaze	3.160 (2.851, 3.538)	0.003 **
left right gaze	3.103 (2.824, 3.438)	0.005 **
eyelid	3.299 (2.915, 3.789)	0.002 **
rigidity	3.137 (2.859, 3.470)	0.002 **
dystonia	2.712 (2.521, 2.933)	0.951
finger tapping	3.064 (2.619, 3.677)	0.142
toe tapping	2.572 (2.270, 2.970)	0.430
apraxia	2.326 (2.092, 2.627)	0.014 *

Item	HR (95% CI)	P values
tremor	2.838 (2.408, 3.448)	0.630
neck	2.700 (2.461, 2.990)	0.890
arising	2.653 (2.405, 2.960)	0.651
gait	3.127 (2.592, 3.914)	0.153
stability	2.498 (2.227, 2.847)	0.195
sitting down	3.163 (2.758, 3.694)	0.029 *
age at baseline	2.727 (2.695, 2.759)	0.598
duration of disease	2.499 (2.422, 2.580)	5.780×10^{-7} ***
sex (male)	3.658 (2.999, 4.623)	0.002 **

*Note. Multivariate Cox proportional-hazards model (forward selection model) results for all items to predict survival using disease progression after the first six-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; knife = using knife and fork, buttoning clothes, washing hands and face; arising = arising from chair; stability = postural stability; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Table 9. Multivariate Cox Proportional-Hazards Model (Forward Selection Model) for all PSPRS Domains to Predict Survival using Disease Progression after the First Six-Months.

Domain	**HR (95% CI)**	**P values**
Cognitive	2.737 (2.662, 2.816)	0.635
Bulbar	3.137 (3.011, 3.272)	5.160×10^{-13} ***
Limb Motor	2.790 (2.711, 2.874)	0.076
Oculomotor	2.890 (2.811, 2.974)	9.800×10^{-6} ***
Gait & Midline	2.763 (2.699, 2.831)	0.176
Urinary	2.853 (2.710, 3.012)	0.065
Sleep	2.883 (2.702, 3.089)	0.077
Age at Baseline	2.728 (2.698, 2.758)	0.523
Duration of Disease	2.500 (2.428, 2.577)	1.510×10^{-7} ***
Sex (Male)	3.781 (3.127, 4.719)	2.870×10^{-4} ***

*Note. Multivariate Cox proportional-hazards model (forward selection model) results for all domains to predict survival using disease progression after the first six-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Prediction of Survival Using Disease Progression After Three-Months.

For items, dysphagia for liquids, sitting down, and disease duration were found to be moderately significant, with p-values between 0.001 and 0.01 (denoted by **) in both forward and backward multivariate Cox proportional-hazards models after the first three months (Table 6, Table 10). Dysphagia for solids, using knife and fork, limb rigidity, voluntary upward saccades, and eyelid dysfunction items were also found to be slightly significant with p-values between 0.01 to 0.05 (denoted by *) in both forward and backward selection models (Table 6, Table 10).

For domains, only the bulbar domain was highly significant (denoted ***) in both selection models with p-values less than 0.001. This significance was not surprising given the frequency of aspiration pneumonias as the final terminal event for most patients. Furthermore, the oculomotor domain was found to be slightly significant (*) in both models, and disease duration was found to be highly significant (***) in the forwards selection model while it was moderately significant (**) in the backwards selection model. Therefore, after a strict Bonferroni correction for multiple significance tests, only the bulbar domain was predictive of survival after three months of disease progression (forward selection p-value: 4.080×10^{-8}; backward selection p-value: 2.430×10^{-8}) indicating that three months may not be enough time to properly assess survival via these PSPRS metrics.

Prediction of Survival Using Disease Progression After Six-Months.

For items, dysphagia for solids and disease duration were found to be highly significant (***) in both forward and backward multivariate Cox proportional-hazards models after the first six months (Table 8, Table 12). Grasping, dysphagia for liquids, limb rigidity,

voluntary downward saccades, voluntary left and right saccades, eyelid dysfunction, and gender were found to be moderately significant (**) in both forward and backward selection models; and voluntary upward saccades and sitting down items were found to be slightly significant (*) in both models (Table 8, 12). Furthermore, the bulbar domain, oculomotor domain, gender, and disease duration were all highly significant (***) in both forward and backward multivariate Cox models. (Table 9, Table 13).

After a strict Bonferroni correction for multiple significance tests, the survival analyses suggest that the dysphagia for solids item (forward selection p-value: 2.394×10^{-4}; backward selection p-value: 2.350×10^{-4}), bulbar domain (forward selection p-value: 5.160×10^{-13}; backward selection p-value: 3.210×10^{-14}), and the oculomotor domain (forward selection p-value: 9.800×10^{-6}; backward selection p-value: 6.920×10^{-6}) may be the most predictive of survival after six months of disease progression.

Chapter IV.

Discussion

There has been a current lack of validated biomarkers in PSP, and at present, therapeutic options for PSP are symptomatic and insufficient. For all the potential therapies, a well-designed human trial would require validated biomarkers. Without them, the results of negative efficacy trials are difficult to interpret (Stamelou and Boxer, 2015). By identifying modifiable risk factors for disease progression, interventions may be designed and treatment strategies may be optimized to help improve patient survival.

The potential implications for identifying valid biomarkers in PSP could also set the stage for the development of diagnostic tools. Misdiagnosis tends to cause suboptimal treatment and care; finding biomarkers can prevent unnecessary care-seeking and costly investigations due to diagnostic uncertainty (Hunter et al., 2015). Hence, the aim of this study was to find modifiable risk factors of disease progression and survival in PSP.

For PSPRS metrics voluntary upward saccades, voluntary downward saccades, and fall items and oculomotor and gait & midline domains had the fastest annual progression rates in both datasets (Figures 1-4). The analysis of the progression rates of each item in the PSPRS was supported by the reported work of Xie et al. (2022). Additionally, both the rates of change and the items of the gait & midline and oculomotor domains revealed respective clusters, indicating that these items have similar underlying mechanisms and may be highly predictive markers of progression (Figures 7-8, Figures 15-16). The PSPRS items and domains that provided the largest relative contributions to

the total PSPRS score were again the gait & midline items (i.e., gait, sitting down, using knife and fork, postural stability, and arising from chair) and the oculomotor domain respectively, while the cognitive domain appeared to have the lowest relative contribution out of all domains (Tables 2-3). These results are consistent with the clinical presentation of many patients who start with ocular motor impairment first, followed by impairment in gait and history, mentation, and lastly bulbar (Brittain et al., 2019). Interestingly, the 10-item Food and Drug Administration (FDA)-proposed scale does not include voluntary eye movement items, which suggests that this scale may not provide an accurate representation of disease progression in PSP.

The falls item in the PSPRS appeared to be a serious limitation and does not show good separation (Figure 9A). Additionally, falls was one of the only items that did not cluster with the rest of the gait & midline items in both rates of change of items and item-versus-item heatmaps (Figures 7-8, Figures 15-16). Even though falls are historical, this item is a problem in the PSP Rating Scale. The frequency of falls is highly dependent on whether patients are using an assistive device. The PSPRS falls item does not adequately capture the use of a cane, walker, wheelchair, or assistance from a caregiver to prevent falls (Bluett et al., 2017). Clarification of this topic may help better understand and capture falls in PSP.

Benzodiazepine derivatives (including lorazepam, temazepam, alprazolam, midazolam, clonazepam, diazepam, tetrazepam, bromazepam, and oxazepam) taken for indications of anxiety and insomnia were found to be associated with a faster disease progression in the Davunetide dataset (Table 4). Observational studies have previously reported associations with benzodiazepine use and an increased risk of falls and fractures

(Markota et al., 2016). Several studies have also found that long-term benzodiazepine users have an increased risk of developing lasting cognitive deficits and dementia (Zhong et al., 2015). However, some case reports of a benzodiazepine related drug, zolpidem, reported improvements in sleep, motor, and voluntary saccadic eye movements in PSP (Cotter & Crimmins, 2010). Interestingly, the benzodiazepine related drug (including zolpidem, zopiclone and eszopiclone) medication class was not significant and was not associated with PSPRS progression in the Davunetide trial. There are pharmacological differences between benzodiazepines and zolpidem: benzodiazepines non-selectively bind and activate all benzodiazepine receptor subtypes, whereas zolpidem selectively activates benzodiazepine receptor 1 (Cotter & Crimmins, 2010). The results found in this analysis and the pharmacological differences suggest that benzodiazepine related drugs and benzodiazepine derivatives may have different underlying mechanisms and effect PSP differently.

The mechanism underlying the negative impacts of benzodiazepines on worsening PSP progression is currently unknown. More research needs to be performed to determine the interaction between benzodiazepines and PSP pathology. Nonetheless, this medication class should be prescribed cautiously to prevent worsening of the disease and alternative medications for treating insomnia and anxiety should be strongly considered for patients with PSP.

Immune system disorders, psychiatric disorders, and renal and urinary disorders were also found to be strongly associated with faster disease progression compared to all other baseline medical history classes in the Davunetide trial (Table 5). In the Davunetide dataset, indications for immune system disorders included allergies (seasonal, multiple,

etc.) and drug hypersensitivity; psychiatric disorders included depression, insomnia, anxiety, affect lability, and personality change; and renal and urinary disorders included urinary incontinence, micturition urgency, pollakiuria, and nephrolithiasis. A scarce amount of literature has been published regarding past medical history of allergies or renal and urinary disorders as risk factors in PSP, due to a lack of clinical data in a large cohort of patients. For psychiatric disorders, anxiety and depression have been linked to an increased risk of diagnosis or a worsening of disease progression in other neurological disorders aside from PSP. A significantly increased risk of developing FTD and AD was observed in patients who had reported anxiety and depression respectively (Rasmussen et al., 2018). Again, more in-depth longitudinal studies need to be performed to validate these results and more trials such as the Davunetide dataset need to be publicly available for researchers to analyze and elucidate results from. Nevertheless, physicians should be cognizant of these medical history classes in patients with PSP or at risk for PSP.

The results of the survival analyses revealed that the dysphagia for solids item and bulbar and oculomotor domains were excellent predictors of survival in PSP patients (Tables 6-13). Gait and balances measures should be theoretically important, given the high rate of injury due to falls in PSP, but surprisingly did not predict survival well. In the future, gait must be measured in a more rigorous way in the PSPRS. As for the bulbar phenotypes, dysphagia has been frequently reported as a predictor of mortality in PSP and other neurodegenerative diseases. Dysphagia was significantly associated with shorter survival and increased mortality in patients with FTD (Grasbeck et al., 2003). Early dysphagia was also found to be a predictor of shorter survival in PSP, and researchers have suggested considering it a possible endpoint in future clinical trials

(dell'Aquilia et al., 2013). In this study, not only were participants with worse dysphagia at baseline progressing faster (Figure 9B), but they also had an increased mortality as well. This concept suggests that the bulbar domain and the dysphagia item in the PSPRS might be strong predictors of both PSP progression and survival, more so than other domains or items in the PSPRS. A continuous effort to study dysphagia or the bulbar domain as potential modifiable risk factors may serve to be highly beneficial given the supportive evidence from this study and prior literature.

In summary, these specific PSPRS items, PSPRS domains, concomitant medications, and baseline medical history classes could be valuable for prediction of disease progression and survival in PSP. However, despite the Davunetide dataset being one of very few clinical trial datasets that contain medication, medical history, and clinical data in a large cohort of participants with PSP, this research study is limited in several ways, both internally and externally.

The internal limitations include the lack of all types of biomarkers i.e., PET, blood-based, CSF biomarkers, etc. in the clinical trial datasets, which could hinder the accuracy of diagnosis. Further, since the sample size was limited to the number of participants in these studies, the generalizability or applicability of the potential biomarkers found in these datasets to all patients with PSP may be questionable. As a retrospective, observational study, both bias and confounding errors could have also impacted the results and prevented establishing any causal relationships between the modifiable risk factors and PSP progression and survival. Finally, autopsy confirmation of PSP diagnosis was lacking in the datasets.

External limitations include an inability to obtain further information from the subjects that participated in these clinical trials, as this study only performed a secondary analysis on previously collected clinical trial data.

The risk factors identified in this secondary analysis require additional large prospective cohort studies with long term follow-up to confirm these findings. It is imperative researchers continue to investigate risk factors to relieve the disease burden and economic costs of this disease, as well as find disease-modifying treatments and targeted therapies for this rare disease population.

Appendix 1.

Additional Tables and Figures

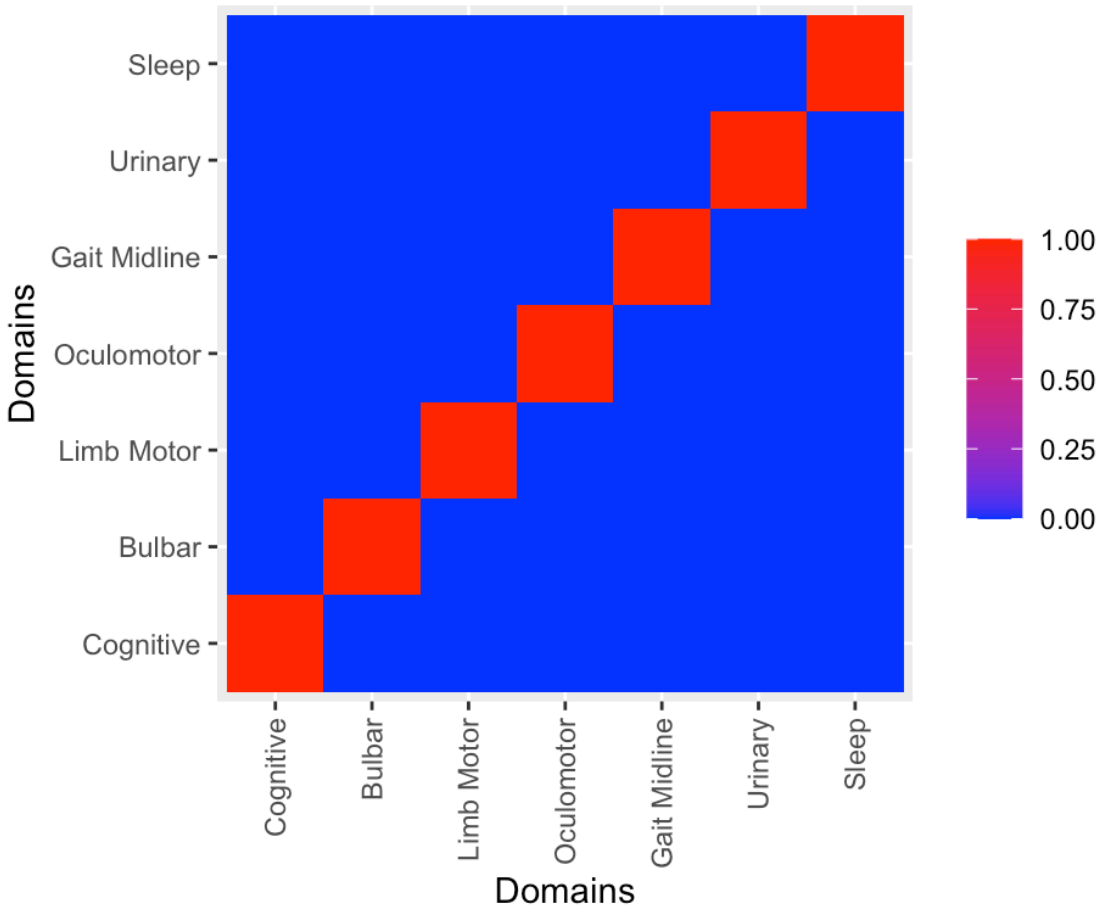

Figure 13. Heatmap of Spearman Correlations Between Domains in the Golbe Dataset.

The Spearman correlations between domains in the Golbe dataset. Different ρ values were represented by different shaded colors. Domains did not show any correlation with one another.

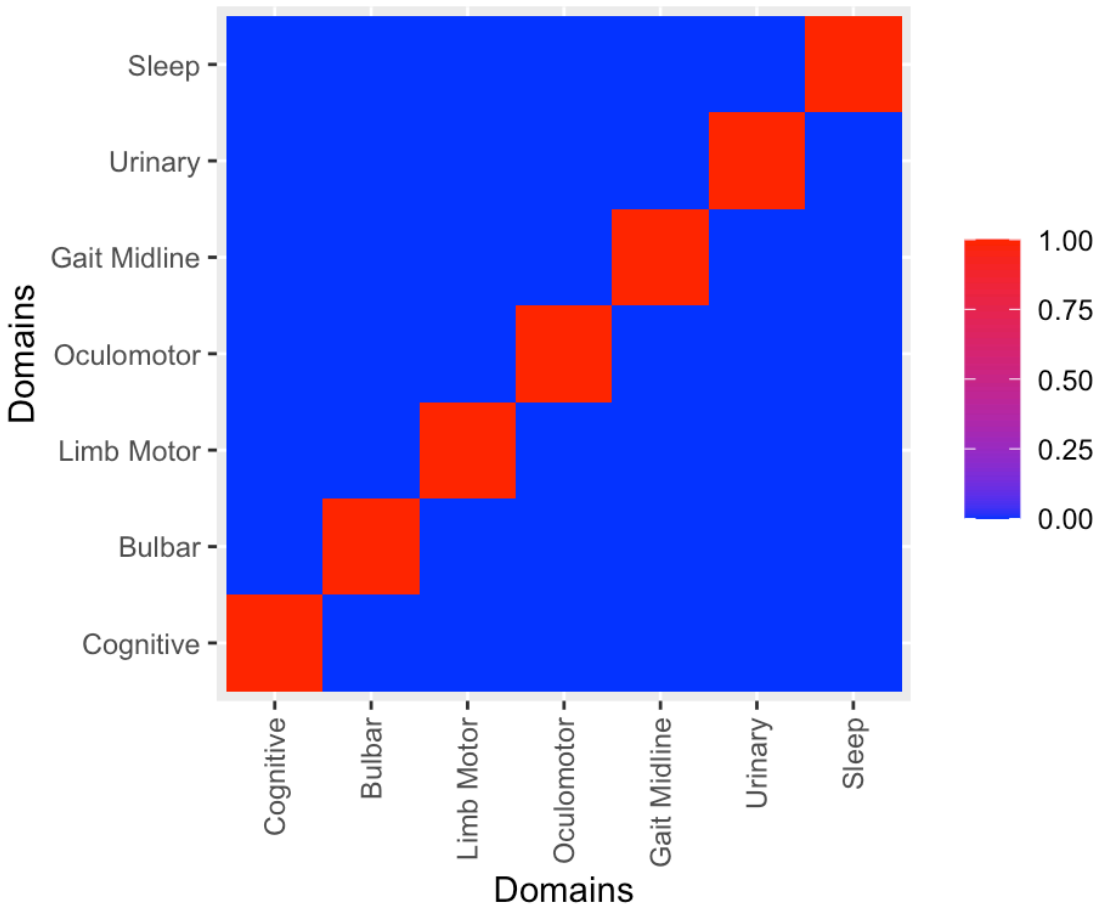

Figure 14. Heatmap of Spearman Correlations Between Domains in the Davunetide Dataset.

The Spearman correlations between domains in the Davunetide dataset. Different ρ values were represented by different shaded colors. Domains did not show any correlation with one another.

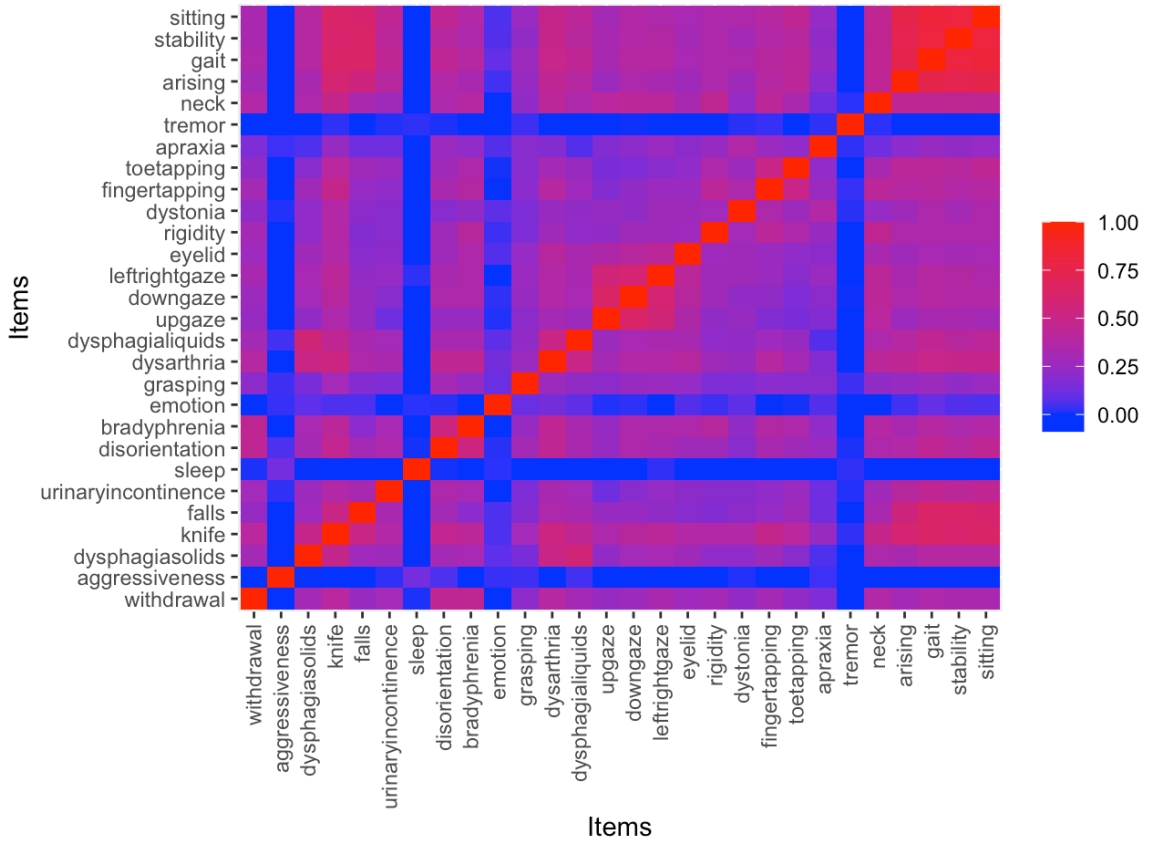

Figure 15. Heatmap of Spearman Correlations Between Items in the Golbe Dataset.

The Spearman correlations between individual items in the Golbe dataset. Different ρ values were shaded different colors, denoted by the figure legend. The item-to-item visualizations show gait & midline and oculomotor clusters as indicated by the red shaded regions. Clustering of arising from chair, gait, postural stability, and sitting down items were visible; and clusters of voluntary upward saccades, voluntary downward saccades, and voluntary left and right saccades were visible. Abbreviations: arising = arising from chair; stability = postural stability; sitting = sitting down; downgaze = voluntary downward saccades; upgaze = voluntary upward saccades; leftrightgaze = voluntary left and right saccades.

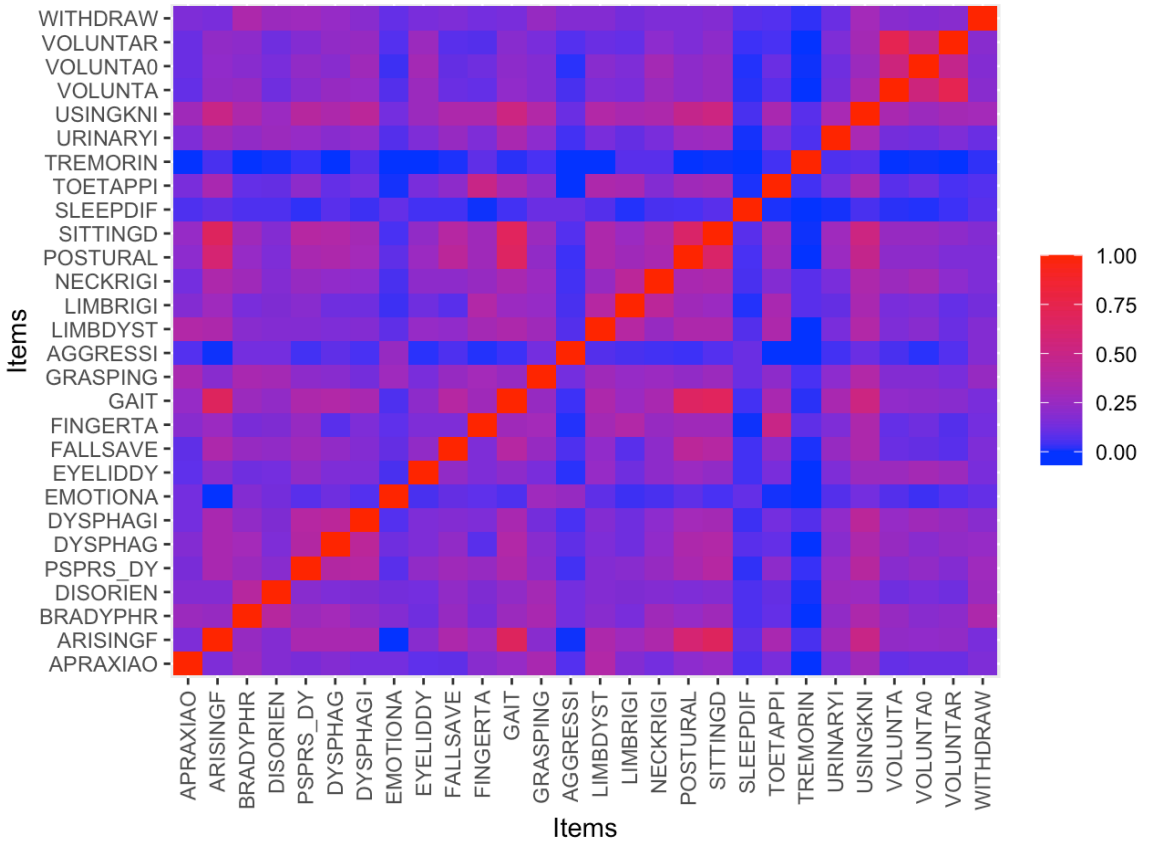

Figure 16. Heatmap of Spearman Correlations Between Items in the Davunetide Dataset.

The Spearman correlations between the individual items in the Davuentide dataset. Different ρ values were shaded different colors, denoted by the figure legend. The item-to-item visualizations show gait & midline and oculomotor clusters as indicated by the red shaded regions. Clustering of postural stability, sitting down, arising from chair, and gait items were visible; and clusters of voluntary upward saccades, voluntary downward saccades, and voluntary left and right saccades were visible. Abbreviations: postural = postural stability; sittingd = sitting down; arisingf = arising from chair; voluntar = voluntary upward saccades; volunta = voluntary downward saccades; volunta0 = voluntary left and right saccades.

Table 10. Multivariate Cox Proportional-Hazards Model (Backward Selection Model) for all PSPRS Items to Predict Survival using Disease Progression after the First Three-Months.

Item	HR (95% CI)	P values
withdrawal	2.341 (1.976, 2.892)	0.153
aggressiveness	2.943 (2.446, 3.678)	0.426
dysphagia solids	3.287 (2.802, 3.951)	0.018 *
knife	3.313 (2.774, 4.080)	0.027 *
falls	2.668 (2.334, 3.116)	0.803
urinary incontinence	2.687 (2.494, 2.912)	0.769
sleep	2.904 (2.643, 3.221)	0.175
disorientation	2.650 (2.384, 2.984)	0.659
bradyphrenia	2.980 (2.605, 3.473)	0.190
emotion	2.649 (2.371, 3.004)	0.674
grasping	3.056 (2.688, 3.531)	0.075
dysarthria	2.983 (2.546, 3.589)	0.265
dysphagia liquids	3.388 (2.938, 3.982)	0.002 **
upgaze	2.334 (2.083, 2.660)	0.024 *

Item	HR (95% CI)	P values
downgaze	3.118 (2.657, 3.756)	0.097
left right gaze	2.881 (2.539, 3.324)	0.384
eyelid	3.378 (2.772, 4.277)	0.030 *
rigidity	3.224 (2.814, 3.762)	0.013 *
dystonia	2.497 (2.268, 2.782)	0.119
finger tapping	2.579 (2.133, 3.271)	0.637
toe tapping	2.499 (2.102, 3.093)	0.411
tremor	3.174 (2.422, 4.515)	0.289
neck	2.945 (2.519, 3.534)	0.334
arising	2.569 (2.246, 3.005)	0.458
gait	3.301 (2.467, 4.853)	0.213
stability	2.306 (1.945, 2.855)	0.122
sitting down	3.614 (2.909, 4.692)	0.008 **
age at baseline	2.727 (2.677, 2.778)	0.745
duration of disease	2.518 (2.402, 2.647)	0.003 **

Item	HR (95% CI)	P values
sex (male)	2.999 (2.345, 4.118)	0.469

*Note. Multivariate Cox proportional-hazards model (backward selection model) results for all items to predict survival using disease progression after the first three-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; knife = using knife and fork, buttoning clothes, washing hands and face; arising = arising from chair; stability = postural stability; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Table 11. Multivariate Cox Proportional-Hazards Model (Backward Selection Model) for all PSPRS Domains to Predict Survival using Disease Progression after the First Three-Months.

Domain	HR (95% CI)	P values
Cognitive	2.775 (2.662, 2.897)	0.335
Bulbar	3.173 (2.997, 3.368)	2.430×10^{-8} ***
Limb Motor	2.784 (2.666, 2.912)	0.282
Oculomotor	2.846 (2.736, 2.965)	0.022 *
Gait & Midline	2.809 (2.713, 2.911)	0.064
Sleep	2.845 (2.611, 3.123)	0.308
Age at Baseline	2.738 (2.694, 2.784)	0.377
Duration of Disease	2.521 (2.415, 2.638)	0.001 **

Domain	HR (95% CI)	P values
Sex (Male)	3.269 (2.575, 4.407)	0.140

*Note. Multivariate Cox proportional-hazards model (backward selection model) results for all domains to predict survival using disease progression after the first three-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Table 12. Multivariate Cox Proportional-Hazards Model (Backward Selection Model) for all PSPRS Items to Predict Survival using Disease Progression after the First Six-Months.

Item	HR (95% CI)	P values
withdrawal	2.544 (2.251, 2.930)	0.340
aggressiveness	2.992 (2.635, 3.455)	0.145
dysphagia solids	3.279 (2.955, 3.674)	2.350×10^{-4} ***
knife	2.792 (2.523, 3.124)	0.619
falls	2.679 (2.443, 2.966)	0.770
urinary incontinence	2.799 (2.656, 2.958)	0.280
sleep	2.884 (2.696, 3.100)	0.086
disorientation	2.551 (2.384, 2.745)	0.088
bradyphrenia	2.828 (2.604, 3.092)	0.359

Item	HR (95% CI)	P values
emotion	2.565 (2.387, 2.773)	0.141
grasping	3.093 (2.829, 3.407)	0.004 **
dysarthria	2.978 (2.667, 3.365)	0.108
dysphagia liquids	3.149 (2.871, 3.483)	0.001 **
upgaze	2.460 (2.285, 2.667)	0.016 *
downgaze	3.161 (2.853, 3.538)	0.003 **
left right gaze	3.103 (2.824, 3.438)	0.005 **
eyelid	3.299 (2.915, 3.788)	0.002 **
rigidity	3.137 (2.859, 3.470)	0.002 **
finger tapping	**3.061 (2.625, 3.658)	0.137
toe tapping	2.572 (2.270, 2.970)	0.431
apraxia	2.324 (2.099, 2.608)	0.009 **
tremor	2.837 (2.408, 3.445)	0.632
neck	2.699 (2.461, 2.989)	0.887
arising	2.653 (2.405, 2.959)	0.649

Item	HR (95% CI)	P values
gait	3.124 (2.593, 3.905)	0.153
stability	2.498 (2.228, 2.847)	0.195
sitting down	3.162 (2.758, 3.691)	0.029 *
age at baseline	2.727 (2.696, 2.759)	0.586
duration of disease	2.499 (2.422, 2.580)	5.760×10^{-7} ***
sex (male)	3.657 (2.999, 4.623)	0.002 **

*Note. Multivariate Cox proportional-hazards model (backward selection model) results for all items to predict survival using disease progression after the first six-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; knife = using knife and fork, buttoning clothes, washing hands and face; arising = arising from chair; stability = postural stability; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

Table 13. Multivariate Cox Proportional-Hazards Model (Backward Selection Model) for all PSPRS Domains to Predict Survival using Disease Progression after the First Six-Months.

Domain	HR (95% CI)	P values
Bulbar	3.143 (3.022, 3.274)	3.210×10^{-14} ***
Limb Motor	2.796 (2.718, 2.878)	0.050 *
Oculomotor	2.892 (2.814, 2.975)	6.920×10^{-6} ***

Domain	HR (95% CI)	P values
Gait & Midline	2.768 (2.704, 2.835)	0.131
Urinary	2.859 (2.716, 3.018)	0.053
Sleep	2.881 (2.701, 3.086)	0.078
Duration of Disease	2.499 (2.427, 2.576)	1.210×10^{-7} ***
Sex (Male)	3.776 (3.124, 4.711)	2.960×10^{-4} ***

*Note. Multivariate Cox proportional-hazards model (backward selection model) results for all domains to predict survival using disease progression after the first six-months. Age at baseline, sex (male), and duration of disease were also included in the multivariate analysis. Abbreviations: HR = hazard ratio; CI = confidence interval; * = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.*

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