Cognitive, Behavioral, and Functional Aspects of Progressive Supranuclear Palsy (PSP)

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Disclosures

- None

Objectives

- 1. Examine the cognitive profile of PSP
- 2. Examine associations of cognition in PSP
- 3. Examine behavior changes in PSP
- 4. Examine functional ability in PSP

Cognition in PSP

- “Subcortical dementia”
- Prominent executive dysfunction
- Slow information processing
- Limited involvement of memory & language

Brown et al, 2010; Gerstenecker et al., 2013; Aarsland et al., 2003; Bak et al., 2005; Grafman et al., 1995; Litvan et al., 1994; Pillon et al., 1991; Pillon et al., 1986

Cognitive Study Methods

- Environmental and genetic risk factors for PSP 5R01AG024040
- 350 PSP patients --NINDS-SPSP Criteria (Litvan et al., 1996)
- MMSE >24
- Dementia Rating Scale – 2 (DRS)
- Frontal assessment battery (FAB)
- California Verbal Learning Test – 2nd Ed. Short Form
- Boston Naming Test

Gerstenecker, A., Mast, B., Duff, K., Ferman, T. J., & Litvan, I., for the ENGENE-PSP Study Group. (2013). Executive Dysfunction is the Primary Cognitive Impairment in Progressive Supranuclear Palsy. *Archives of Clinical Neuropsychology, 28,* 104-113.

Demographic	Mean (SD)
Age	68 (6.6)
Sex	184 M, 166 F
Education	15.0 (3.5)
Disease Duration	3.8 (1.6)
UPDRS Total	52.7 (18.2)
PSP-RS Total	36.9 (11.4)

Performance on the DRS-2, FAB, and BNT

Measure	Mean Score Raw scores Z-scores	% Impaired at 5th percentile	% Impaired at 1st percentile
DRS-2 Test/Subtest			
Total Score	125.9 (11.6)		
	6.7 (4.0)	42.6	22.9
Attention	34.9 (2.1)		
	10.1 (2.6)	6.0	2.9
Initiation/	28.9 (5.9)		
Perseveration	5.5 (2.9)	54.0	30.9
Construction	5.0 (1.5)		
	7.9 (2.9)	24.6	14.6
Conceptualization	34.7 (3.7)		
	8.8 (2.6)	8.6	2.6
Memory	22.4 (2.6)		
	8.8 (2.6)	19.3	4.3
Frontal Assessment	13.1 (3.1)		
Battery	-2.8 (3.4)	63.4	53.7
Boston Naming Test	51.8 (8.6)		
	10.3 (4.1)	13.1	7.1

Measure	Mean score	% Impaired at 5th Percentile	% Impaired at 1st Percentile
Trial 1	4.2 (1.4) -1.2 (1.4)	26.8	25.4
Trial 2	5.6 (1.5) n/a		
Trial 3	6.2 (1.6) n/a		
Trial 4	6.5 (1.6) -0.7 (1.3)	22.3	12.0
Total Recall	22.7 (5.3) 41.5 (14.5)	23.1	15.1
SDFR	5.9 (2.0) -0.4 (1.3)	13.2	4.3
LDFR	5.1 (2.3) -0.3 (1.1)	8.3	2.3
LDCR	5.5 (2.0) -0.4 (1.3)	13.1	7.7

# of Tests Impaired	Frequency at 5th Percentile	Percentage (%) at 5th Percentile
0	84	24.0
1	107	30.6
2	99	28.3
3+	60	17.1

Conclusions

- Almost 75% PSP pts with MMSE >24 have at least one test impaired.
- Executive dysfunction is the major neurocognitive impairment (FAB and DRS Initiation/Perseveration) even at early disease stage.
- Relatively strong short and long delayed free recall and little additional benefit from cueing.
- Executive dysfunction was associated with numerous parkinsonian symptoms.
- Cognition should be assessed in this patient population.

Behavioral Abnormalities

- Why do behavior changes matter?
  - Differential DX
    - In one study, PSP patients were differentiated from patients with a more classical “cortical” dementia in up to 85% of cases using only neuropsychiatric profiles (Litvan et al., 1996).
  - Apathy and depression are often confused in PSP, which can lead to unnecessary and unproductive treatment with antidepressants (Litvan et al., 1996).
  - Quality of life for both patient and caregiver.
    - Patients with more severe neuropsychiatric symptoms are reported as more burdensome by their caregivers, contribute to greater levels of depression in their caregivers, and are at a greater risk for institutionalization (Goetz and Stebbins, 1993; Uttl et al., 1998)

Methods

- Same as for cognitive study except sample size was smaller (154).
- The Neuropsychiatric Inventory (NPI; Cummings et al., 1994) assesses both the frequency and severity of behavioral abnormalities across 10 domains: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior.
- Sleep/nighttime behaviors and appetite/eating also assessed but not included in NPI Total score.
- Caregiver form

Gerstenecker, A., Duff, K., Mast, B., & Litvan, I., for the ENGENE-PSP Study Group. (2013). Behavioral Abnormalities in Progressive Supranuclear Palsy. *Psychiatry Research*, *210,* 1205-1210.

Demographic	Mean±SD (Range)
Age (years)	68.0 ±6.6 (53-87)
Sex	89 M, 65 F
Education (years)	15.3±3.5 (8-20)
Symptom duration (years)	3.8±1.6 (6-10)
UPDRS Total	57.8±18.8 (16-102)
PSP-RS Total	37.1±11.6 (13-70)
DRS-2 Total	123.7±11.7 (88-144)
FAB Total	12.5±2.7 (5-18)
MMSE	26.7±2.26 (24-30)

NPI Domain	Mild N (%)	Moderate N (%)	Severe N (%)	Total N (%)
Apathy/Indifference	42 (27.3)	40 (26.0)	13 (8.4)	95 (61.7)
Depression/Dysphoria	64 (41.6)	25 (16.2)	1 (0.6)	90 (58.4)
Sleep/Nighttime	31 (20.1)	35 (22.7)	14 (9.1)	80 (51.9)
Appetite/Eating	16 (10.4)	31 (20.1)	14 (9.1)	61 (39.6)
Agitation/Aggression	39 (25.3)	15 (9.7)	1 (0.6)	55 (35.6)
Irritability/Lability	33 (21.4)	16 (10.4)	2 (1.3)	51 (33.1)
Disinhibition	28 (18.2)	19 (12.3)	2 (1.3)	49 (31.8)
Anxiety	23 (14.9)	13 (8.4)	1 (0.6)	37 (23.9)
Elation/Euphoria	13 (8.4)	7 (4.5)	1 (0.6)	21 (13.5)
Aberrant Motor	9 (5.8)	7 (4.5)	3 (1.9)	19 (12.2)
Hallucinations	12 (7.8)	5 (3.2)	0 (0.0)	17 (11.0)
Delusions	7 (4.5)	1 (0.6)	0 (0.0)	8 (5.1)

Results

- Neither demographics (i.e., age or education) nor disease severity variables (i.e., age of onset or disease duration) were significantly correlated with any NPI domain or NPI Total score.
- General cognitive function (DRS-2 Total) was not associated with any NPI variable at the .01 level.
- NPI Disinhibition was significantly correlated with PSP-RS Total.
- No other associations between NPI variables and measures of Parkinsonian severity were significant at the 0.01 level.
- NPI Depression and NPI Apathy were not associated (r=0.12).

Education about Apathy is Important

- Apathy is particularly distressing for family members and caregivers (Brown and Pluck, 2000) and lead to symptoms being misinterpreted as depression.
- This may lead to an unnecessary initiation of antidepressant medication.
- Families may believe that the patient is not as interested in family activities and interactions because of something they are doing wrong.
- Education about apathy in PSP may provide some comfort to patients and their caregivers.

Apathy and Depression

- Since depression and apathy can appear similar and co-occur in neurodegenerative disorders, some have posited that these might represent a single construct, whereas others think that they are two clearly different phenomena (Levy et al., 1998).
- Apathy and depression were not statistically correlated, sharing only 1% of variance.

Apathy and Depression

- Furthermore, only 13 patients were rated as exhibiting moderate to severe symptoms of both apathy and depression.
- Finally, anxiety is commonly associated with depression but not apathy and this pattern of association was observed in the current study.
- These findings seems to suggest that depression was seen as distinct from apathy in the caregivers who provided ratings for the NPI.

Depression

- Depression prevalence was unexpectedly high in comparison to prior estimates (Litvan et al., 1996; Litvan et al., 1998; Aarsland et al., 2001).
- In PSP, disruptions to the cortical circuits associated with depression are far less affected than those associated with apathy (Agid et al., 1987; Javoy-Agid et al., 1994; Litvan et al., 1996).

Depression

- Depressive symptoms may not solely be a function of brain changes associated but also related to functional consequences (e.g., decreased mobility and independence).
- Treatments including psychotherapy and antidepressant medication may be effective for PSP patients reporting significant symptoms of depression.
- Caregivers can be utilized to aid in these treatments.
- In turn, the quality of life of both patient and caregiver may be modifiable.

Functional Ability

- Two types: Basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs)
- ADLs
  - Related to self-care (e.g., bathing, dressing, grooming)
- IADLs
  - Related to autonomy and independence (e.g., financial management, medication management, driving)

Functional Ability

- Current diagnostic classification systems for dementia require evidence of functional decline attributable to cognitive impairment exclusive of motor impairment.
- Diagnosis of comorbid dementia in PSP has treatment implications (i.e., medication options and referrals for supportive services).

Functional Ability

- Investigations into functional ability in PSP have relevance for clinical trials.
  - Disease-modifying clinical trials may be affected by the inclusion of patients with PSP that already have dementia.
  - FDA gives preference to outcome measures that are tied to functional ability.

Assessing Functional Ability in PSP

- Examples of current methods of assessing functional ability in PSP include
  - PSP-RS ADL (Golbe & Ohman-Stickland, 2007)
  - UPDRS-ADL (Fahn & Elton, 1987)
  - SE-ADL (Schwab & England, 1969)
- Functional disability in PSP is primarily due to physical disability.
- Contribution from cognition is low.

Duff, K., Gerstenecker, A., & Litvan, I., for the ENGENE-PSP Study Group. (2013). Functional Impairment in Progressive Supranuclear Palsy. *Neurology, 80,* 380-384.

Methods/Results

- Administered performance-based and caregiver-report IADL measures to 26 participants (13 PSP and 13 caregivers).
- The performance-based IADL measures tapped medical decision-making, financial decision-making, and the ability to communicate and use a phone.
- Results showed that IADL functioning is impaired in over 80% of people with PSP.
- Medical decision-making is particularly impaired, with impairment rates similar to PDD.

Gerstenecker, A., Grimsley, L., Otruba, B., Cowden, L. Perez, S., & Roberson. Caregiver-Report of IADL Functioning in PSP. In review.

Gerstenecker, A., Grimsley, L., Otruba, B., Cowden, L. Perez, S., & Roberson. Medical Decision-Making in PSP. In review.

Results

- Financial decision making was also poor, and people with PSP appear to be susceptible to financial fraud/scams.
- Although not as frequently impaired as medical and financial decision making, more than 50% of the PSP sample was unable to use a phone to call 911 and accurately convey the emergency.
- Caregiver-report was not significantly correlated with any IADL measure or with cognitive performance.

Conclusions

- Caregiver-report is not a reliable method of evaluating daily functioning in PSP.
- This hampers clinicians ability to accurately diagnose dementia or make recommendations about appropriate level of support.
- Also, current methods of tapping daily functioning in drug trials are suboptimal.
- Caregivers need education about level of IADL impairment in PSP.

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