UNIVERSITÀ DEGLI STUDI DI SALERNO

DIPARTIMENTO DI MEDICINA, CHIRURGIA ED ODONTOIATRIA
"Scuola Medica Salernitana"

DOTTORATO DI RICERCA IN MEDICINA TRASLAZIONALE DELLO SVILUPPO E DELL'INVECCHIAMENTO ATTIVO

Curriculum: Marcatori molecolari, radiologici, clinici e cognitivo-comportamentali dello sviluppo e del declino funzionale

Ciclo: XXXII

Coordinatore: Prof. Palmiero Monteleone

TESI DI DOTTORATO IN:

Cognitive and behavioral features in atypical parkinsonian syndromes

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A.A. 2018-2019

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Al "ricercatore curioso"
che ha finalmente imparato
ad osservare il mondo,
senza l'eccesiva
pretesa di controllarlo.

Chapter 1

ATYPICAL PARKINSONIAN SYNDROMES

1. Introduction:atypical parkinsonisms

Parkinsonism is a clinical syndrome, which is characterized by bradykinesia, rigidity, rest tremor and postural instability. The most common cause of this syndrome is idiopathic Parkinson disease (PD) but there are several other important etiologies that must be considered, indeed, a smaller but significant number of patients present with a parkinsonian syndrome that has atypical features such as early dementia, frequent falls, ocular dysmotility, prominent dysautonomia, or ataxia. These syndromes typically involve multisystem degeneration and are referred to as atypical parkinsonian syndromes or atypical parkinsonisms (AP) (Keener and Bordelon, 2016; McFarland, 2016). Multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy Bodies (DLB) are included in AP; which are secondary causes of parkinsonism. These various disease entities may be distinguished based on key clinical features, which is critical for the purposes of diagnosis, treatment and prognosis (Keener and Bordelon, 2016) .

Although increasingly recognized, AP remain challenging to diagnose and are underrecognized due to overlap with other parkinsonisms. Atypical parkinsonian syndromes first have to be differentiated from PD. In this regard certain features or “red flags” have been identified that help distinguish atypical parkinsonian

syndromes from PD: rapid disease progression, early gait instability and falls, absence or paucity of tremor, autonomic failure and poor or absent response to levodopa, including pain/dysesthesia. Additional features may include oculomotor abnormalities, pyramidal tract or cerebellar signs (ataxia), prominent dysautonomia, severe dysarthria or dysphonia, laryngeal stridor, myoclonus, alien limb, apraxia, and early dementia(Mulroy et al., 2019). Furthermore in PD, onset of parkinsonism is mostly unilateral, and over time asymmetric bilateral symptoms develop. If tremor is the dominant symptom, especially as regular 'pill rolling' resting tremor, atypical parkinsonism is unlikely. The levodopa response is good in PD, while it is limited or even absent in atypical parkinsonism. Hyperkinesia and dyskinesias are seen in later stages of PD, but not in atypical parkinsonism. The disease course is far more benign in PD. Cerebellar symptoms and extrapyramidal motor signs are not present in typical PD, while autonomic symptoms do occur, primarily cardiovascular (orthostasis). Olfactory dysfunction is common in PD, rare in CBD and PSP and mildly impaired in MSA (Deutschländer et al., 2017).

Therefore atypical parkinsonismis umbrella term and it refers to a clinical presentation with various causes, emphasizing the clinical commonality of diseases in which atypical parkinsonism can present. This term is, generally, useful for describing the phenomenology of a movement disorder and to classify patients according to their clinical presentation. In contrast to this classification per phenotype, a classification per pathology is needed when it comes to understanding the pathogenesis and designing and delivering disease-modifying therapeutic interventions. Clinico-pathological correlation studies have revealed enormous clinical heterogeneity and vast clinical overlap in pathologically defined diseases related to atypical parkinsonism. Thus, the classification of patients with atypical parkinsonism per phenotype has limited validity for predicting the underlying pathology (Respondek et al., 2019). Against AP are neurodegenerative disorders with intracellular deposition of amyloidogenic proteins. Clinicopathologic terms are also being used to describe AP in the clinic because of the diagnostic uncertainty and overlap of symptoms (**Fig. 1**). Specifically, DLB and MSA (as well as PD) are characterized by the abnormal deposition of the protein α-synuclein and therefore referred to as synucleinopathies, in PSP and CBD the tau

protein causes damage and these entities are therefore referred to as tauopathies. In PD and DLB, α-synuclein aggregates are found in neurons and in MSA these are found primarily in oligodendrocytes. In PSP and CBD, tau aggregates affect neurons, but also oligodendrocytes and astrocytes. The morphology of astrocytic tau deposits is what distinguishes PSP from CBD (Levine et al., 2016).

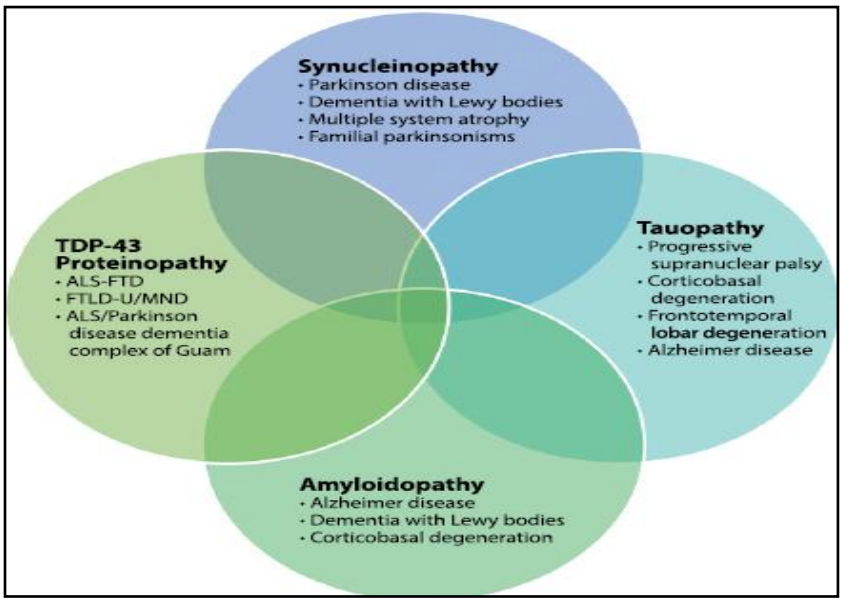

Fig. 1: Clinicopathologic overlap of neurodegenerative proteinopathies (readjusted by McFarland, 2016).
ALS = amyotrophic lateral sclerosis; FTD = frontotemporal dementia; FTLD-U = frontotemporal lobar degeneration with ubiquitin; MND = motor neuron disease; TDP-43 = TAR DNA binding protein 43.

2. Progressive supranuclear palsy

Over 50 years ago Steele, Richardson and Olszewski described for the first time Progressive supranuclear palsy (PSP)(Richardson et al., 1963).

PSP is the most common form of atypical parkinsonism, comprising about 5% to 6% of those patients presenting with parkinsonism. The average age of onset is typically in the sixties (average age of 63 to 66 years) and the mean survival from diagnosis is reported between 5 to 8 years. Originally the estimated prevalence and annual incidence of PSP is about 5 per 100,000 in individuals between the ages of 50 and 99 years, but is likely higher due to misdiagnosis and underrecognition (Batla et al., 2010). Today, after the first decade of systematic studies, estimations

of its prevalence varied according to the exact methodology used and ranged from 1.4 per 100,000 in earlier to 6.5 per 100,000 in more recent reports. Its incidence has been estimated to be 1.1 cases per 100,000 person-years.These values reflect however only PSP with Richardson's syndrome (RS). In a recent study in Japan that also assessed cases with PSP and progressive gait freezing (PSP-PGF), the prevalence of PSP was estimated at 17.9 per 100,000.Recent estimations of incidence, ranging from 0.14 to 1.2 per 100,000 person-years, do exist, but they also reflect the incidence of RS rather than PSP(Stamelou et al., 2019).

Hallmarks of the disease include prominent, early postural instability, unexplained falls, vertical supranuclear palsy and progressive dementia. A key feature of PSP includes inability to perform volitional saccades and progressive supranuclear ophthalmoparesis. Although limitation of upgaze is often described as a sign of PSP, it is nonspecific and can be seen in other neurodegenerative disorders as well as in aging (Batla et al., 2010).

In 1996 the National Institute of Neurological Disorders and Stroke (NINDS) and the Society for PSP (SPSP) international workshop proposed criteria for the diagnosis of classic PSP (Richardson syndrome- PSP RS) (Litvan et al., 1996). The criteria for possible or probable PSP included a progressive disorder with onset after the age of 40 with postural instability, significant falls, slowing of vertical saccades, or vertical gaze palsy. Definite PSP added the requirement of pathologic evidence. Supportive findings included symmetric rigidity, diminished response to levodopa, and early cognitive impairment. Factors excluding the diagnosis of PSP were encephalitis, focal brain lesion, hallucinations, dysautonomia and alien limb syndrome. Cerebellar features were also previously included as exclusionary, but a recent description of a cerebellar variant of PSP has called this exclusion into question (Kanazawa et al., 2009).

The diagnosis of PSP is further complicated by its heterogeneous presentation, resulting in increasing recognition of clinical variants or phenotypes (Respondek et al., 2014). In classic presentations, the diagnosis of Richardson syndrome is relatively straightforward. However, at least five phenotypic variants have recently been described: PSP-parkinsonism, PSP–pure akinesia with gait freezing, PSP–corticobasal syndrome (PSP-CBS) (or primary nonfluent aphasia), PSP–behavioral variant of frontotemporal dementia (FTD) and two other possible PSP variants with

features that overlap with either primary lateral sclerosis (PLS) or cerebellar ataxia.

The definition of PSP is continually undergoing revision because the clinical diagnostic criteria, published in 1996 by the National Institute of Neurological Disorders and Stroke/Society for PSP, have excellent specificity, but their sensitivity is limited for variant PSP syndromes with presentations other than Richardson's syndrome (Hoglinger et al., 2017). An important advance has been the development of the new International Parkinson's and Movement Disorder Society (MDS) Criteria for the Diagnosis of PSP that recognize early, "suggestive" forms and operationalize diagnosis of non-Richardson's PSP phenotypes. These new research criteria provide a framework for incorporating MRI, physiological and fluid biomarker in diagnostic decision making and novel clinical trial designs (Litvan et al., 2016b).

After revision, clinical predominance types are determined based on the combination of clinical features and these include:PSP with Richardson's syndrome (PSP-RS), PSP with predominant ocular motor dysfunction (PSP-OM), PSP with predominant postural instability (PSP-PI), PSP with predominant parkinsonism(PSP-P), PSP with predominant frontal presentation (PSP-F), PSP with progressive gait freezing(PSP-PGF), PSP with predominant CBS(PSP-CBS) and PSP with predominat speech/language disorder (PSP-SL).Patients with possible PSP-SL or PSP-CBS also qualify for the diagnosis of a probable 4R-tauopathy. Specifically, PSP-PGF is longer disease duration (11-15 years) and PSP-P is the most common variant of PSP and patients are also frequently levodopa responsive, life expectancy in PSP-P is also typically longer than in Richardson syndrome, averaging 9 or more years from diagnosis; PSP-CBS is one of the rarest presentations of PSP andPSP-F is also a rare variant of PSP (Hoglinger et al., 2017).

Furthermore the MDS-PSP clinical diagnostic criteria are stratified by diagnostic certainty and may therefore be used for different purposes. Indeed definite PSP can only be diagnosed by neuropathological examination at present, probable PSP is diagnosed in the presence of a combination of clinical features that may not be very sensitive for PSP, but are considered to be highly specific, thus being ideally suited for therapeutic and biological studies, where it is important to exclude non-PSP

from the subject group and possible PSP" is diagnosed in the presence of clinical features that substantially increase sensitivity, but at the possible cost of decreased specificity. Finally, the conditionsuggestive of PSP has been newly introduced in the MDS-PSP criteria and represents subtle early signs of PSP, but do not meet the threshold for possible or probable PSP, and are suitable for early identification of individuals in whom the diagnosis may be confirmed as the disease evolves, thereby justifying close clinical follow-up examinations, especially in longitudinal observational studies to further characterize the natural history of PSP with the overall goal of improving diagnosis of patients in early-stage disease (Hoglinger et al., 2017).

Briefly, on pathophysiology, the hallmark of PSP is abnormal deposition of tau and the tufted astrocyte is pathognomonic but other features include coiled bodies, neuropil threads, pretangles, and neurofibrillary tangles. Tau pathology generally spares the cortex and involves the basal ganglia, dentate, pontine, and oculomotor nuclei. There is associated gliosis and degeneration that is marked by midbrain atrophy, loss of pigmented cells in the substantia nigra, and atrophy of the subthalamic nucleus, superior cerebellar and middle cerebellar peduncles, dentate nucleus, and frontal cortex (Stamelou et al., 2010).

3. Multiple system atrophy

Multiple system atrophy (MSA) is a sporadic, adult-onset, neurodegenerative disorder and it is the most rapidly progressive of the synucleinopathiesthat is characterized by a variable combination of autonomic failure, parkinsonism and ataxia (Fanculli et al., 2019). Patients with MSA have a mean age at onset of 55–60 years, and an average survival from the onset of motor symptoms of 8–9 years, although some pathology-proven cases survived > 15 years.Median age of onset for MSA is younger than that of PSP and CBD. No MSA cases have been identified younger than age 30.Selective atrophy and neuronal loss in striatonigral and olivopontocerebellar systems underlie the division into two main motor phenotypes of MSA-parkinsonian type (MSA-P) and MSA-cerebellar type (MSA-C), also according to the predominance of parkinsonism or cerebellar impairment (Laurens

et al., 2017).In the Western hemisphere, MSA-P is more common than MSA-C. Age at onset, prevalence of cardiovascular autonomic dysfunction, sleep disorders, and retinal abnormalities are similar in both phenotypes. Specific neuroimaging markers differ between the cerebellar and parkinsonian phenotypes, as well as the degree of sudomotor dysfunction which may be more severe in patients with MSA-P and urogenital dysfunction which may occur earlier in patients with MSA-C (Palma et al., 2018).

Isolated autonomic failure and REM sleep behavior disorder are common premotor features of MSA. Beyond the core clinical symptoms, MSA manifests with a number of non-motor and motor features (Fanciulli et al., 2019). Specifically, among symptoms of cardiovascular autonomic failure, orthostatic hypotension (OH) is the most frequent clinical feature (Pavy-Le Traon et al., 2016).

Sleep breathing disorders and sudden death during sleep are frequent in MSA. A large retrospective study in 136 MSA patients reported an association between stridor onset within the first 3 years of disease and shorter survival, whereas the overall survival between patients with and without stridor was not different (Giannini et al., 2016).

Response to anti-parkinsonian medications, particularly levodopa, is usually sub-optimal and often transient. Cold hands and feet are a typical feature of the disease. A bluish discoloration of the feet is frequently seen in wheelchair-bound patients, probably due to venous stasis. All patients with MSA have gastrointestinal, cardiovascular, urogenital and thermoregulatory abnormalities but the severity of symptoms varies among patients (Fanciulli and Wenning, 2015). Indeed, the diagnosis of probable or possible MSA according to the 2008 consensus criteria relies on either the presence of OH or urinary dysfunction indicating pathological involvement of autonomic neurons (Gilman et al., 2008). Early and severe autonomic failure appears to be associated with poorer prognosis.

MSA may be difficult to distinguish clinically from other disorders, particularly in patients at the early stages of the disease. An autonomic-only presentation can be indistinguishable from pure autonomic failure (PAF). Patients presenting with parkinsonism may be misdiagnosed as PD. The reverse also occurs; approximately 20% of patients with a clinical diagnosis of MSA turn out to have

PD or DLB at autopsy. Patients presenting with the cerebellar phenotype can mimic other adult-onset ataxias due to alcohol, chemotherapeutic agents, lead, lithium, and toluene, or vitamin E deficiency, as well as paraneoplastic, autoimmune, or genetic ataxias (e.g., spinocerebellar ataxias, fragile X–associated tremor ataxia syndrome, or late-onset Friedreich ataxia) (Palma et al., 2018).

Current consensus guidelines include neuroimaging criteria for the diagnosis of possible MSA (Gilman et al., 2008). These include the presence of atrophy of the putamen, middle cerebellar peduncle, pons or cerebellum on brain magnetic resonance imaging (MRI), and putamen, brainstem or cerebellum hypometabolism on brain fluorodeoxyglucose (FDG) positron emission tomography (PET), as well as dopaminergic denervation on PET or single photon emission computed tomography (SPECT) (Palma et al., 2018).

4. Corticobasal degeneration

Corticobasal degeneration (CBD) is an atypical parkinsonian syndrome with predominant involvement of the cortex and basal ganglia that presents with varied phenotypes and it is probably the most challenging disorder to diagnose antemortem (Grijalvo-Perez et al., 2014) .

CBD is increasingly also recognized to present with features that may overlap with fronto-temporal dementia (FTD), primary progressive aphasia (PPA), Alzheimer disease (AD), posterior cortical atrophy and PSP. According to Alexander et al.(2014) CBD often presents with a corticobasal syndrome including impairments of movement and cognition. However, patients with similar corticobasal syndromes can have neurodegenerative pathologies that are not CBD. In addition, patients with CBD may present with aphasia or behavioural change.

Typically, marked asymmetry of involvement is the most striking feature and helps differentiate CBD from other degenerative disorders. The asymmetric hand clumsiness is followed by early bradykinesia, a frontal syndrome, tremor, and rigidity (Wenning et al., 1998). The mean onset of disease occurs in the sixth decade, and prognosis is generally poor with a mean survival of about 7 years from diagnosis. In more detail, typical features include marked asymmetry, focal

rigidity, coarse rest/action tremor, limb dystonia (followed by contractures), alien limb phenomenon, hand, limb, gait, or speech apraxia, myoclonus, cortical sensory loss, language deficits, frontal/cortical dementia, oculomotor dysfunction (gaze palsy, impaired convergence), bulbar impairment, postural instability, gait difficulty, hyperreflexia, and extensor plantar response. Poor levodopa response tends to occur. Ideomotor apraxia, myoclonus, asymmetric rigid-bradykinetic syndrome, and later-onset gait/balance disturbance have been reported as the best predictors for CBD diagnosis. Ideomotor apraxia is defined by an inability to perform a skilled motor task despite having intact language, motor, and sensory function. Examples include inability to imitate gestures or mime a certain task (eg, use a screwdriver or cut with a pair of scissors). This type of apraxia can be difficult to distinguish from limb-kinetic apraxia, which is frequently seen in parkinsonisms, but is independent of modality (imitation versus miming). Peculiar to CBD, alien limb phenomenon appears as abnormal grasping, posturing, or spontaneous levitation of an arm or leg, but can also include pursuit or avoidance of a tactile stimulus in the opposite or contra lateral limb. Dementia in CBD is actually a late feature with typically preserved semantic memory. Neuropsychiatric testing often shows a fronto-striatalparietal predominance with deficits in attention, concentration, verbal fluency, language, praxis, and executive and visuospatial function. Cortical findings such as aphasia, limb apraxia and graphesthesia depend on the hemisphere predominantly affected (McFarland et al., 2016).

The clinical diversity of CBD and mimicry by non-CBD pathologies hinders accurate diagnosis.

Current criteria for the clinical diagnosis of pathologically confirmed CBD no longer reflect the expanding understanding of this disease and its clinicopathologic correlations. Aninternational consortium of behavioral neurology, neuropsychology and movement disorders specialists developed new criteria based on consensus and a systematic literature review. Combined with consensus, 4 CBD phenotypes emerged: corticobasal syndrome (CBS), frontal behavioral-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and progressive supranuclear palsy syndrome (PSPS). These were classified into probable and possible CBD. Probable CBD has a more stringent criterion and is focused towards identifying patients for research, whereas possible CBD criteria

allows more flexibility by removing restrictions on age, family history, and presence of tau mutations to increase clinical detection of tauopathies. Specifically, probable CBD criteria require insidious onset and gradual progression for at least 1 year, age at onset ≥50 years, no similar family history or known tau mutations, and a clinical phenotype of probable CBS or either FBS or naPPA with at least 1 CBS feature. The possible CBD categoryuses similar criteria but has no restrictions on age or family history, allows tau mutations, permits less rigorous phenotype fulfillment, and includes a PSPS phenotype. When applied to neuropathologically proven cases of CBD, the criteria were found to be lacking diagnostic specificity and although a higher number of potential cases may be detected, prediction of CBD pathology was found to be no different from prior criteria. Overall, accurate clinical antemortem prediction of CBD pathology is severely lacking, and not advanced by the current diagnostic criteria (Armstrong et al., 2013).

5. Dementia with Lewy Bodies

Lewy body dementia or disease (LBD) is an early-onset, rapidly progressive dementia associated with progressive cognitive decline, behavioural changes and movement disorder. It is the second most common form of neurodegenerative dementia, after Alzheimer disease (AD)and has similar features to other dementias (McKeith et al., 2017). Approximately 1–2% of those aged above 65 years are diagnosed with DLB worldwide, affecting approximately 5% of all dementia cases in those over the age of 75. Its incidence is 0.7–1.4 new cases/100,000 person-years or 3.5/100,000 person-years (Hogan et al., 2016). For typical DLB, the average survival time from the beginning of symptoms is 5–8 years (Williams et al., 2006).

Dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities, is an essential requirement for DLB diagnosis. Measures of attention/executive function that differentiate DLB from AD and normal aging, in fact disproportionate attentional, executive function and visual processing deficits relative to memory and naming are typical in DLB (McKeith et al., 2017). The clinical criteria for DLB in addition to early dementia include: parkinsonism that is

coincident with or follows dementia onset, fluctuating cognition, awareness, or alertnessand recurrent visual hallucinations. Additional features include gaitinstability, falls, syncope or transient loss of consciousness, delusions/paranoia,depression, REM sleep behavior disorder, and neuroleptic sensitivity. A combination of dementia and psychosis in general is considered a poor prognostic predictor in this population (McKeith et al., 2005).DLB fluctuations are typically delirium-like, occurring as spontaneous alterations in cognition, attention, and arousal and they are the best predict DLB when they are present early. They include waxing and waning episodes of behavioral inconsistency, incoherent speech, variable attention, or altered consciousness that involves staring or zoning out. Recurrent, complex visual hallucinations occur in up to 80% of patients with DLB and are a frequent clinical signpost to diagnosis. They are typically well-formed, featuring people, children, or animals, sometimes accompanied by related phenomena including passage hallucinations, sense of presence, and visual illusions.Patients are typically able to report these experiences, as are observant caregivers. Patient responses to their hallucinations vary both in degree of insight and emotional reaction to them (McKeith et al., 2017). A diagnosis of clinically probable DLB requires two or more core clinical features to be present, with or without indicative biomarkers, or the presence of only one core clinical feature but with one or more indicative biomarkers (McKeith et al., 2017).

Together with Parkinson's disease dementia (PDD), it is classified as one of the Lewy body dementias, which are characterised by the presence of alpha-synuclein deposits within neurons known as LBD with Lewy bodies is notoriously difficult to diagnose, averaging greater than 18 months and reviews by multiple specialists to correctly diagnose(Goodwin et al., 2019).

DLB and PDD are important dementia syndromes that overlap in many clinical features, genetics, neuropathology, and management. DLB and PDD, which share many clinical, neurochemical, and morphological features, have been incorporated into DSM-5 as two separate entities of major neurocognitive disorders with Lewy bodies. Despite clinical overlap, their diagnosis is based on an arbitrary distinction concerning the time of onset of motor and cognitive symptoms, namely as early cognitive impairment in DLB and later onset following that of motor symptoms in PDD. Their morphological hallmarks - cortical and subcortical α-

synuclein/Lewy body plus β-amyloid and tau pathologies - are similar, but clinical differences at onset suggest some dissimilar profiles (Jellinger et al., 2018). Intravitam PET and postmortem studies have revealed a more pronounced cortical atrophy, elevated cortical and limbic Lewy body pathologies, higher Aβ and tau loads in cortex and striatum in DLB compared to PDD, and earlier cognitive defects in DLB. Conversely, multitracer PET studies have shown no differences in cortical and striatal cholinergic and dopaminergic deficits. Based on international consensus, DLB is diagnosed when cognitive impairment precedes parkinsonian motor signs or begins within 1 year from its onset, whereas in PDD, cognitive impairment develops in the setting of well-established PD. DLB patients will also develop parkinsonism of increasing severity over the years, although 25% of them never develop parkinsonian symptoms.

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Chapter II

COGNITIVE AND BEHAVIORAL PROFILE IN ATYPICAL PARKINSONISMS

1. Introduction

1.1 Biomarkers and neuropsychology

The discovery of biomarkers is among the most important goals in research in atypical parkinsonisms (AP) and neurodegenerative diseases in general. Over the past decade, several potential neuroimaging, biological and neurophysiological biomarkers have been described as potentially helpful in differentiating parkinsonian syndromes. However, an important lesson learned from early studies is that the diagnostic value of these biomarkers cannot be established without adequately powered studies in autopsy confirmed cases. Therefore, there is urgent need for diagnostic biomarkers that can detect pathology in very mildly symptomatic or presymptomatic individuals, allowing for earlier diagnosis and intervention with potentially disease modifying therapies. Such biomarkers could permit expansion of therapeutic studies to earlier disease stages in these patients. Furthermore, biomarkers that can demonstrate pharmacodynamic effects of new therapies on their intended targets are needed to support clinical trials (Boxer et al., 2017).

Among biomarkers, also neuropsychological tests could be considered; they could be an accurate, standardized and easy to use premortem screening method. Neuropsychology is a distinctly transdisciplinary service and although the roles of

neuropsychologists have evolved over time, the primary purposes for clinical neuropsychological assessment have remained fairly constant, to: detect neurological dysfunction and guide differential diagnosis, characterize changes in cognitive strengths and weaknesses over time, and guide recommendations regarding everyday life and treatment planning. With the advent of increasingly sensitive and multimodal neurologic biomarker data, neuropsychological assessment shifted from its original role in "finding the lesion" to in-depth characterization of the patterns arising from disruptions in brain-behavior relationships. Indeed, neuropsychological batteries were originally constructed with the goal of identifying brain dysfunction, but a prominent emerging role of the neuropsychologist is to monitor syndrome progression or recovery via repeated evaluations. As such, quantifying what constitutes significant change on a test battery is another relatively recent advance in this empirical assessment approach (Casaletto and Heaton, 2017).

Neuropsychological testingplay yet an important role in the diagnosis of neurological diseases by documenting cognitive deficits, for example in AD (Sano, 2006). Improved neuropsychological assessment and characterization of domains also in APmay assist in better identifying the pathophysiology of deficits, perhaps in combination with new technologies such as functional imaging. Improved assessment tools for specific cognitive domains should assist in identifying a broad range of cognitive deficits at earlier stages and ultimately lead to more effective interventions for a wider range of cognitive deficits.

1.2 Background: Cognitive and behavioral profile in atypical parkinsonisms

The cognitive profile of patients with atypical parkinsonism (AP)differs according to the sub-diagnosis (Burrel et al., 2014).

Dividing the AP by sub-diagnosis, it has been proven that 10% of patients with PSP experience cognitive symptoms and 70% develop dementia during the course of the disorder (Daniel et al., 1995; Bensimon et al., 2009). Generally, behavioral disorders (apathy, irritability and impulsivity), cognitive dysfunctions, alterations of memory, language, visuo-spatial and spatial cognition are structured. Three

quarters of PSP patients have executive deficits (O'Keeffe et al., 2007; Gerstenecker et al., 2013), one third of patients experience episodic memory, short-term memory and/or working memory problems and reduced visuo-spatial functions (Bak et al., 2005; Brown et al., 2010; Pillon et al., 1995; Robbins et al., 1994). There are bradyphrenia, problem solving and set shifting difficulties (Pillonet al., 1991; Magherini et al., 2005). Patients diagnosed with MSA exhibit cognitive disturbances ranging from a single domain alteration to a multiple domain one, with a prevalence of mild cognitive decline of 22%, up to a frank dementia, whose prevalence is estimated at 31% (Wenning et al., 1997; Brown et al., 2010). Motor impairment appears to be a predictor of the severity of cognitive impairment (Brown et al., 2010; Kawamura et al., 2010). Frontal/executive functionsis the most involved cognitive domain in patients with MSA, which deteriorates rapidly with greater alterations found in fluency tests (Soliveri et al., 2000; Lange et al., 2003); less frequent, but still present, are the alterations of memory, of attention and of visuo-spatial and visuo-constructive functions (Soliveri et al., 2000; Lange et al., 2003 Bak et al., 2006; Brown et al., 2010); language is mostly spared. Patients diagnosed with MSA-P (parkinsonian variant) have mainly attention, working memory and spatial visual problems and in 40% of cases the problems are attributable to the domain of executive functions, with reduction of speed of thought, difficulty of problem solving, difficulty in mental flexibility and abstract reasoning, persevering tendencies, alterations in fluency tests, difficulty in recalling verbal material (Lange et al., 2003; Balas et al., 2010; Siri et al., 2013). Patients with MSA-C (cerebellar variant) exhibit significant impairment of executive skills (Dubois et al., 2000), reduced efficiency in verbal fluency tests and stimulus learning deficits (Chang et al., 2009; Balas et al ., 2010). CBD, on the other hand, is characterized by a wide range of cognitive and behavioral disorders (Mathew et al., 1968); patients with this diagnosis may frequently present progressive aphasia or multiple domain cognitive decline (Turaga et al., 2013; Kertesz et al., 2000; Mathew et al., 2011). For the aforementioned pathology, changes in executive functions are described and memory (Turaga et al., 2013; Kertesz et al., 2000; Bak et al., 2005; Kertesz et al., 2010), however, the deficits found for language, visual-spatial skills and social cognition are more distinct (Kertesz et al., 2000; Kertesz et al., 2010). The 11% of

patients in the early stage experience speech disorders, up to 70% in the more advanced stages. Alterations of visual-spatial abilities are very present and the possible development of Balint syndrome with simultaneous agnosia, oculomotor apraxia, and optic ataxia is also found(Mendez et al., 2000; Mathew et al., 2012; Shelley et al., 2009; Burrell et al., 2013; Bak et al., 2005; Graham et al., 2003a; Graham et al. , 2003b; Tang-Wai et al., 2003).Patients with DLB show typical elements of subcortical dementia, such as distractibility, ideational slowdown, visual hallucinations, significant fluctuations, verbal working memory deficit, visual-perceptive and attentional-executive deficits (Toraboschi et al., 2006; Aarsland et al., 2010; Kehagia et al., 2010). The cognitive profile of patients with LBD is very heterogeneous (Aarsland et al., 2010) and specifically executive deficits, such as difficulties in selective attention, working memory, mental flexibility, planning and learning, can be prevalent (Kehagia et al., 2010); in 74% of cases, visuospatial and constructive disturbances are found in the initial phase of the disease (Toraboschi et al., 2006).

Defining the neuropsychological profiles of patients is important for a detailed intra-AP framework, for identification of phenotypes and for characterization of patients with typical and atypical syndrome, but there are few studies specifically comparing the neuropsychological profiles of patients with typical and atypical parkisnonsim. In this regard, Fiorenzato et al. (2016) stressed the roule of verbal fluency dysfunctions, particularly phonemic, that have been reported as distinct cognitive deficits vs PD and MSA and found that the phonemic fluency subitem included in MoCA-test is sensitive in detecting cognitive deficits in PSP, while MMSE-test is less helpful (Fiorenzato et al. 2016; Rittman et al. 2013). Moreover, according to the criteria used by Litvan to identify dementia and MCI in PD (2012), Fiorenzato et al. (2019) found that MSA and PSP patients, despite similar disease duration, showed different distribution of cognitive states at baseline. Specifically authors found that in PSP sample, 22% was classified as cognitively normal, 61% MCI and 17% as dementia. At follow-up, two PSP patients with MCI converted to cognitive normal state and 17% to dementia as opposed to 25% of MSA patients, who had converted to MCI, but none to dementia. Overall, these findings suggest a different pattern of cognitive progression, wherein PSP has the most severe and rapid cognitive decline. MoCA, verbal fluencies, Stroop test, Digit

Span Sequencing, Benton's Judgment of Line Orientation test and Visual Object and Space Perceptionappeared the most sensitive in showing differences between these parkinsonian syndromes (Fiorenzato et al., 2019).

2.Objectives

From November 2016 to September 2019, at the University Hospital of Salerno and in collaboration, where necessary, with other italian centers, data collection and processing work was carried out on a sample of healthy subjects (HC) and patients with movement disorders, divided into patients with Parkinson's disease (PD), Multi-Systemic Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and CorticoBasal Syndrome (CBS).

Specific work objectives were:

1) investigation of the neuropsychological and behavioral profile of patients with atypical parkinsonism, divided according to their respective clinical phenotypes;

2) investigation of the evolution over time of the neuropsychological and behavioral profile of patients with atypical parkinsonism;

3) identification and characterization of the alteration of global cognitive state, of the mild cognitive impairment- single domain (MCI-sd), of the mild cognitive impairment - multiple domain (MCI-md) and of the normal cognition (NC) of patients with atypical parkinsonism;

4) comparison of neuropsychological and behavioral aspects with healthy subjects and patients with Parkinson's disease; intra-group comparison of the neuropsychological profile between PSP- Cortico Basal Syndrome phenotype and CBS and MSA-Parkinsonian and cerebellar phenotypes;

5) validation of a new language screening battery for neurodegenerative diseases;

6) investigation of language domain in the sample of patients with PSP and MSA with directives of clinical use of the instrument;

7) investigation and validation of questionnaires for measuring the quality of life in patients with PSP and their respective caregivers;

8) investigation of gender differences in MSA patients.

3. Patients and methods

3.1 Total sample

The sample was divided into two macro groups, such as patients and healthy subjects recruited at the University Hospital of Salerno and patients and subjects reculted for multicentric studies. Particularly, at the University Hospital of Salerno we recruited 55 patients with MSA, 59 with PSP, 50 HC, 55 with PD and 5 with CBS. In multicenter studies, 162 caregivers (29 belonging to University Hospital of Salerno), 190 PSP-patients (62 belonging to University Hospital of Salerno) and 134 HC (35 belonging to University Hospital of Salerno) were recluted.

3.2 Procedure

Patients underwent a comprehensive neuropsychological andneuropsychiatric battery at baseline (T0) and 6 or 12 months follow-up (T1) evaluation, where possible. We compared patients with atypical parkinsonism with HC and patients with PD and different intra-group phenotypes.

3.3 Neuropsychological tools

There are many validated neuropsychological tests that are used in the scientific literature. Generally a complete evaluation includes at least two tests that evaluate the domain of memory, executive, visuo-spatial, attentional and language functions. The scales of evaluation of functional autonomy must be used and optionally behavioral and neurological scales could be used in addition to the neuropsychological tests (Litvan et al., 2012).
Tests used in this thesis work are listed and described below.

Global screening, memory, visuo-spatial, exectutive, attention domains

- *Montreal Cognitive Assessment (MoCA):* it is a rapid screening tool, which investigates eight cognitive domains such as, verbal memory immediate and deferred recall, visual-spatial skills, executive functions, attention, concentration, working memory, thelanguage and space-time orientation (Santangelo et al., 2015).

- *Mini Mental State Examination (MMSE):* is a quick and simple screening tool, consisting of 30 articles. Through the analysis of temporal space, short-term memory and a long verbal term, attention, the naming of objects, spontaneous writing and the copy of a geometric figure, people are distinguished with and without cognitive impairment. The score is between 0 and 30 and below 23.8 we speak of global cognitive efficiency; the test is correct based on schooling and age (Flostein et al., 1975).

- *Immediate and deferred re-enactment test of Rey's 15 words (15-RAWLT)*: assesses the ability to learn and long-term verbal memory; it consists of a list of 15 words. In the immediate re-enactment test, the subject is invited to recall as many words as possible read by the examiner, without respecting the order of presentation; the reading of the list is repeated 5 consecutive times, the examiner must record the words and the order of the re-enactment from time to time asking the subject to also report the words previously said. The deferred re-enactment test is foreseen after a time interval of about 15 minutes during which visuospatial tests are administered; in this case the subject is asked again to recall the greatest number of words belonging to the list read several times previously, without in this case there being a further repetition of the same (Caltagirone et al., 1995).

- *Short story test (Prosa Test):* assesses the ability to learn and recall semantically structured verbal material. The story consists of 26 elements and is read before and after the immediate re-enactment; the deferred re-enactment is requested 10 minutes after the immediate production of the content. The score is the sum of the two re-enactments (De Renzi et al., 1977).

- *Gesture imitation test:* evaluates aspects of ideational and ideo-motor praxis of the upper limbs. The subject is asked to reproduce 24 movements, performed by the examiner, chosen on the basis of 3 dimensions: finger or whole hand movements, to maintain a certain position or sequence, a significant or meaningless gesture. Up to 3 executions are possible (De Renzi et al., 1986).

- *Constructive apraxia of Milan:* it is a visuo-spatial task that explores object building skills. 7 progressively more complex geometric designs are presented to the subject and asked to copy the stimuli in the lower part of the sheet respecting their dimensions and ratios. The score attributed to each sub-test ranges from 2 to 0 (2 for well-made drawings, 1 for defective copies and 0 for unrecognizable copies or closing-in) (Spinnler and Tognoni, 1987).

- *Benton orientation line test (BJLO*):evaluates the visual-spatial skills and consists of 30 tables, on which 2 lines with different inclination are drawn to be compared with a model of lines arranged in a radial pattern, in order to highlight the correspondence. The raw score ranges from a minimum of 0 to a maximum of 30; scores less than 26 are considered below average performance, scores between 15 and 18 indicate the presence of moderate deficits and a score below 15 is indicative of severe dysfunction (Benton et al., 1992).

- *Phonemic fluency*: it is a test that evaluates mental flexibility and the inability to generate an unusual research strategy; the subject is asked to produce in 1 minute the largest number of words that begin with a specific phonological stimulus, such as F-A-S (Caltagirone et al., 1995).

- *Semantic fluency:* it is a test that assesses access to the lexicon via semantics; the subject is asked to produce in 1 minute the largest number of words belonging to a certain category, such as car brands and fruits (Novelli et al., 1986).

- *Frontal assessment battery (FAB):* is a screening battery used to evaluate global executive functionality through a series of cognitive and behavioral tests. It consists of six sub tests: conceptualization of similarities, lexical fluency in phonemic mode, motor programming (Luria series), response to conflicting instructions, go-no go task, prehension behavior (Iavarone et al., 2004).

- *Clock drawing test, recall (CDT):* evaluates the ability to represent mental and plan. Inviting the patient to consider a circumference drawn on a sheet like the face of a clock, he is asked to insert the numbers inside and then the hands that mark

11:10. The maximum score obtainable is 10 and is attributed on the basis of the presence and distribution in the dial of the numbers, the position and length of the hands (Siciliano et al., 2016).

- *Trail Making Test (TMT):* evaluates visual exploration, divided attention and attentive set-shfting. It is composed of 2 parts; TMT-A is a visuo-spatial research task, which requires you to combine the numbers circled and arranged on a sheet in a random order in increasing order; the TMT-B part instead evaluates the subject's ability to switch from a numerical to an alphabetic stimulus, respecting its progressive order. It is a time trial and a greater result corresponds to a greater inefficiency of the front functions (Giovagnoli, 1996).

- *Stroop test:* it consists of three subparts;the first is a list of color names to be read, the second is a list of colored circles to be named and the third is a list of color names written in a different ink so the subject must say the name of the ink without readingthe word (Barbarottoet al., 1998).

- *Rey complex figure test (copy and deferred):* it is a test that involves the copy of a complex figure consisting of 18 elements that after 15 minutes must be recalled without the aid of the stimulus.

Language domain:

- *Neuropsychological Examination of Aphasia battery (ENPA***):** it is a battery used for the analysis of speech disorders.the sub-test investigating the auditory comprehension of sentences on a matrix of two morpho-syntactically similar images and repetition of non-words was used here (Capasso et al., 2001).

- *Token Test*: is a tool used for the evaluation of the understanding of spoken language. The examiner places tokens of different shape, color and size in front of the patient in order to make him perform progressively more complex commands (Carlomagno et al., 2007).

- *Screening forAphasia in NeuroDegeneration (SAND) battery:*
Published in *Neurological Sciences* 2017; 38(8):1469-1483.

It is based on the Mini Standard Language Examination proposed by Garrard and Ahmed (2012). The SAND battery aims at the detection of language disorders through the assessment of different components of language. It includes nine subtests: picture naming, word and sentence comprehension, word and sentence repetition, reading, semantic association, writing, and picture description.
The implementation of normative data was necessary for the use of this battery in clinical practice, allowing to control for the impact of age, education, and gender on performance in each of the tests. The normative sample included 134 native Italian speakers (56 males), with a mean age of 63.28 (SD = 11.19; range 45–85 years) and a mean of 11.04 years of education (SD = 4.95; range 2–25) (Catricalà et al., 2017).

Functional autonomy:
- *Daily life activities (ADL):* evaluation scale that accurately investigates 6 basic activities, such as bathing, dressing, toileting, moving around, urinary and faecal continence, eating. The scores assigned are dichotomous, 1 is used to indicate a state of independence, 0 is used to indicate a state of dependence (Katz et al., 1963).

- *Instrumental activities of daily life (IADL):* it is a rating scale that investigates the ability to perform activities that are also carried out by elderly subjects, necessary for the maintenance of one's independence. For each item the answer can be 1 / independent or 0 / dependent. The areas investigated are, use of the telephone, shopping, preparing food, housekeeping, linen, means of transport, responsibility for the use of drugs and ability to handle money (Lawton and Brody, 1969).

Behavioral domain:
- *Beck Depression Inventory II (BDI-II):* Indicator of the presence and intensity of depressive symptoms, it is developed after the publication of the DSM-IV.It consists of 21 questions, each answer is associated with a value ranging from 0 to

3.Replies should be for the past two weeks.A higher score indicates more severe depressive symptoms (Kjaergaard et al 2014).

-*Apathy Evaluation Scale (AES):* Evaluation scale consisting of 18 items, investigating the cognitive, behavioral and emotional components of apathy. The subject must choose between 4 response alternatives (very-quite-little-not at all) (Santangelo et al., 2014)

- *PSP- Quality of life (PSP-Qol):*there are two versions. The patient's version has 45 items and cargiver' s version has 26 items, the answers, for both versions, are placed on a 6-point Likert scale. Evaluate the quality of life in the last 2 weeks (The EuroQol Group, 1990).

- *Hospital Anxiety and Depression Scale (HADS):* Self-administered scale that explores generalized anxiety and depression. Anxiety symptoms are classified separately from depression symptoms: Odd items are representative of anxiety; Even items are representative of depression (<emotional aspects; does not include physical and cognitive symptoms or suicidal ideation). It excludes important items to identify the severity spectrum of depression, including suicidal ideation, psychotic features and vegetative symptoms. It excludes most somatic symptoms. More suitable for mild to moderate depression than for a more severe depression. Composed of 14 items evaluated on a 4-point scale (from 0, absence of the symptom, to 3, maximum severity) (Zigmond et al., 1983).

Neurological features:

- *Unified Parkinson's Disease rating Scale (UPDRS):* it is a clinical scale used to quantify the motor disability and functional loss of patients with Parkinson's disease (Fahn et al., 1987).
- *Unified Multiple System Atrophy Rating Scale (UMSARS):* it is a clinical scale used to quantify the motor disability and functional loss of patients with Multi Systemic Atrophy (Wenning et. Al., 2004).
- *Rating scale for progressive supranuclear palsy (PSP-RS):* it is a clinical scale used to quantify the motor disability and functional loss of patients with Progressive Supranuclear Palsy (Golbe et al., 2007).

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4. Comparative cognitive and behavioral profile between PD, MSA and PSP

Published in *Journal of Neurology* 2018; 265(11):2602-2613.

4.1Abstract

Background: Parkinsonian syndromes are characterized by a wide spectrum of non-motor symptoms. A few studies explored cognitive deficits and neuropsychiatric symptoms in atypical parkinsonism compared to Parkinson's disease (PD). The study was performed to identify cognitive and neuropsychiatric differences between PD, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) and to evaluate the influence of clinical features, depressive symptomatology and apathy on cognitive performances in the three groups.

Methods: Fifty-five PD, 44 MSA and 42 PSP patients underwent cognitive tests assessing attention, language, memory, visuospatial and executive functions as well as scales assessing depression and apathy. Out of these patients, 20 PD, 20 MSA and 20 PSP patients were selected to be matched for age, education and global cognitive status. Within each whole patients group, correlational analysis was performed between clinical, behavioural and cognitive parameters.

Results: The main difference among the groups matched was on cognitive tests exploring verbal learning, executive and linguistic functions. The PSP group was more impaired than the PD and MSA groups on cognitive tests assessing executive functions. On the other hand, MSA group obtained similar cognitive performance to the PD group. As to behavioural symptoms, in whole PSP and MSA groups, apathy and depression were more severe than in PD group, while apathy (but not depression) were more severe in the PSP group as compared to the MSA group.

Conclusions: The present study underlined the pervasiveness of cognitive deficits, apathy and depressive symptoms in PSP, whereas little cognitive differences were found between PD and MSA. The findings indirectly supported a dysfunction of prefronto-subcortical circuitries (i.e., dorsolateral prefrontal and limbic circuits) in PSP and PD. Cognitive similarities between MSA and PD reinforced the pivotal role of altered basal ganglia and corresponding frontal deafferentation in the occurrence of the cognitive deficits.

4.2. Introduction

Parkinsonian syndromes include Parkinson's disease (PD) as well as atypical parkinsonism such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration, all considered proteinopathies with distinctive features [1].

Neuropsychological profile in PD is very heterogeneous and is characterized mainly by frontal-executive dysfunction. Notwithstanding, a subgroup of PD patients more prone to develop dementia shows prominent cholinergic cortical dysfunctions [2]. As opposite to PD, few studies explored cognitive deficits associated with atypical Parkinsonism. The majority of available data focused on the comparison between either MSA or PSP and either PD or healthy subjects, with very few studies examining similarities and differences in cognitive functions by a simultaneous comparison of PD, MSA and PSP subjects [3,4,5,6]. In addition, the examination of language and memory abilities has been largely neglected in favour of the assessment of executive and visuospatial functions [7,8,9,10]. Robbins et al. [10] found impaired executive functions in subjects with Parkinsonism compared with a control group but did not analyse in detail the differences between each group of Parkinsonian subjects. Monza et al. [9] compared small groups of PSP, MSA and PD patients matched for demographic and disease-related variables (although with longer disease duration for PD) and showed ideomotor apraxia, frontal and visuospatial dysfunctions in PSP patients compared to MSA and PD patients. As a drawback, this study lacked of assessments for attention and language domains. Other studies found significant differences comparing PD, MSA and PSP patients on frontal and verbal fluency tasks [7, 8]. These studies were limited by the sample size and the lack of assessments for other cognitive domains besides executive functions.

Neurobehavioural disturbances represent frequent non-motor complains in Parkinsonian syndromes. While an extensive amount of the literature is available for PD, little is known about clinical correlates and nature of the psychopathology (particularly depression and apathy) in atypical Parkinsonism compared to PD [11, 12].

Aims of the present study were to identify differences and similarities in cognitive and neuropsychiatric symptoms of PD and atypical Parkinsonism (i.e., MSA and

PSP) and to investigate the possible influence of clinical parameters, depressive symptomatology and apathy on cognitive performances in each of the three patient groups. A better characterization of the behavioural abnormalities and/or cognitive deficits in distinct types of Parkinsonian syndromes can potentially improve the clinical care and management of these patients. Moreover, better neuropsychological profiling in Parkinsonian syndromes might help to provide a basis on which to plan any cognitive remediation interventions.

4.3 Methods

Participants

In the present study, we enrolled consecutive outpatients with clinically probable diagnosis of idiopathic PD, MSA, and PSP according to published clinical criteria (for PD [13]; for MSA [14]; for PSP: [15]). All the participants were recruited at our Center for Neurodegenerative Diseases. We excluded patients affected by (1) radiological structural brain abnormalities not compatible with a diagnosis of a neurodegenerative syndrome, (2) a history of alcohol or substance abuse, (3) previous head trauma with loss of consciousness, with significant neurological or psychiatric comorbidities that might confound the results (4) any diseases causing significant physical disabilities impacting a neuropsychological assessment.

Participants gave their written informed consent to the study which was approved by the appropriate ethics committee and therefore was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Material and procedures

Demographic aspects, disease duration, levodopa equivalent daily dose (LEDD; [16]), functional autonomy in activity of daily living (ADL [17]) and instrumental ADL (IADL [18]), were collected; severity of motor symptoms was evaluated by Unified Parkinson's Disease Rating Scale part III (UPDRS-III [19]) for PD group, by Unified Multiple System Atrophy Rating Scale (UMSARS [20]) for MSA group, and by Progressive Supranuclear Palsy Rating Scale (PSP-RS [21]) for PSP group.

Neuropsychological assessment: Cognition

All participants underwent the Italian version of the Montreal Cognitive Assessment (MoCA [22]) and standardized neuropsychological tasks for assessment of several frontal/executive functions (by Trail Making Test-B and B-A, TMT, [23] to evaluate set shifting; phonological fluency test [24] to evaluate cognitive flexibility; interference task of Stroop Color-Word Test, Stroop [25] to evaluate inhibitory control; Clock Drawing Test, CDT [26]; immediate and delayed copying tests of Rey–Osterrieth complex figure test [27] to evaluate spatial organization and planning); memory (verbal long-term memory by immediate and delayed recall of the Rey's auditory 15-word learning test, RAVLT [24]); language (Semantic fluency task [28]; auditory and visual comprehension of single word tasks, and words, non-words and sentence repetition tasks [29]); visuospatial perceptual and constructional functions (by Benton Judgment of Lines Orientation Task, BJLOT [30], and Constructional Apraxia Task, CAT [31]).

Neuropsychiatric assessment

To assess depressive symptomatology and apathy, all patients completed the Italian version of the Beck Depression Inventory-II (BDI-II [32]) and Apathy Evaluation Scale (AES), validated in Parkinsonian syndromes [33].

4.4 Statistical analysis

An a priori power analysis was performed with G*Power 3.1 by setting the following parameters: probability level (a) of 0.05, statistical power ($1 - b$) of 0.80, large effect size Cohen's f of 0.40 for the Kruskal–Wallis test, and rho of 0.5 for Spearman's correlation analysis. According to Pitman [34], the sample size required for a nonparametric test is determined by multiplying the sample size calculated for the equivalent parametric test by a correction factor.

Differences in the distribution of categorical variables among groups were assessed by means of Chi square. Group comparisons on demographic, clinical, cognitive and behavioural variables were performed by nonparametric tests (Kruskal–Wallis H test to compare three samples, and the Mann–Whitney U test to compare two samples) to avoid biases due to the small sample size. To avoid type-II errors

we used a conservative statistical approach by applying Bonferroni's correction ($p = 0.0026$).

The correlations between neuropsychological performances (raw scores) and clinical parameters, depressive symptoms and apathy in each patient group were performed by Spearman's rank-order correlation. The significance level was set at pre-specified threshold ($p < 0.010$). Analyses were performed with SPSS version 21 (SPSS Inc. Chicago, IL, USA).

4.5 Results

Fifty-five (16 females) PD, 44 (22 females) MSA patients and 42 (17 females) PSP patients were enrolled; these groups differed on age and education but not gender ($\chi^2 = 4.546$, $p = 0.103$): PSP was the oldest while MSA was the youngest group. As for educational level, PD patients had higher educational level than PSP patients (Table 1). All PD patients were on levodopa reporting a significant improvement in motor symptoms. Sixteen/42 PSP and 10/44 MSA patients were not taking levodopa preparations. Functional autonomy was greater in PD compared with PSP and MSA; the PSP group showed the worst functional autonomy score. The mean UPDRS-III score for PD group was 14.6 ± 9.5; the mean PSP-RS score for PSP group was 40.9 ± 17.9; the mean UMSARS-I, II and IV score for MSA group were 22 ± 8.9, 23.2 ± 0.9; 2.7 ± 0.9. Finally, the H test showed significant differences among the three groups on total MoCA (Table 1). The descriptive of demographic, clinical and neuropsychological parameters of each patients group is reported in Supplementary Material 1.

Since PD, PSP and MSA patients showed significant differences on age, education and MoCA, we selected eligible cases by scrutiny of these abovementioned parameters to control for the potential bias. Moreover, since the a priori power analysis revealed that at least 60 individuals (20 individuals for each group) for the Kruskal–Wallis test were needed to attain a large effect size at a statistical power of 0.80 and an alpha level of 0.05, we selected 20 patients for each group who were matched as closely as possible between them for demographic features and global cognitive functioning. The three groups of PSP patients, PD patients and MSA patients were compared on cognitive and neuropsychiatric scores.

Neuropsychological assessment: Cognition

The results showed that the three groups matched for age, education and MoCA score had significantly different performance on immediate RAVLT, phonological fluency tests, immediate copy of ROCF, TMT-B, TMT:B-A, time to complete the Stroop test (Table 2). In particular, PSP patients had lower score on all cognitive tests than PD and had poorer performance on Stroop test and TMT than MSA; finally PD patients obtained similar cognitive performance to MSA patients. The percentage of the patients with pathological performance with respect to Italian normative data within each group and between groups was reported in Table 3.

In the three groups, the linguistic and executive domains were the most damaged cognitive domains (Fig. 1). Moreover, as for executive functions, in PD and MSA group spatial planning was the most damaged executive function. In PSP group, both spatial planning and set shifting were the most damaged executive functions (Fig. 2).

Neuropsychiatric assessment

The three groups had significantly different scores on AES and BDI (Table 2). PD patients had lower scores than MSA and PSP patients on depression and apathy scales; MSA patients were less apathetic than PSP patients. Taking into account screening cut-off values of BDI-II and AES, we found that the proportion of depressed MSA patients was higher than that of depressed PSP and PD patients, whereas the proportion of apathetic patients was higher in PSP groups than that in MSA and PD patients. In Fig. 3, pie charts report the percentage of patients with pure apathy, patients with pure depression, patients with apathy and depression, patients without apathy and depression for MSA, PSP and PD groups. We found that the percentage of patients with "pure apathy" was higher in PSP group than in MSA and PD groups, and the percentage of patients with co-occurrence of apathy and depression was similar in PSP and MSA groups.

Correlational results within whole PSP, MSA and PD groups

The a priori power analysis revealed that at least 29 participants for the Spearman's correlation analysis were needed to attain a large effect size at a statistical power of 0.80 and an alpha level of 0.05. Therefore, on the basis of power-analysis results,

we performed correlational analysis on each whole patients group (PD group = 55 patients; MSA group = 44 patients; PSP group = 42 patients).

Correlational results between clinical aspects and cognitive parameters

Whereas in PD and MSA group clinical parameters did not correlate with any cognitive scores, in PSP group, PSP-RS tended to correlate with semantic fluency (rho = − 0.509, $p = 0.013$) score.

Correlational results between clinical aspects and neuropsychiatric parameters

In PD group, clinical parameters did not correlate with any behavioural scores. In MSA group, we found a significant correlation of UMSARS-I with BDI-II (rho = 0.491, $p = 0.008$) and ADL (rho = −0.664, $p < 0.001$), and also a significant correlation of part II and IV of UMSARS-II with ADL scores (rho = − 0.571, $p = 0.001$; rho = − 0.522, $p = 0.004$). In PSP group, PSP-RS score correlated with AES (rho = 0.599, $p = 0.003$), ADL (rho = − 0.616, $p = 0.002$), and IADL (rho = − 0.644, $p = 0.001$).

Correlational results between behavioural and cognitive parameters in each patient group

In PD group, AES score significantly correlate with score on phonological fluency task (rho = −0.371, $p = 0.008$) and number of errors in Stroop test (rho = 0.412, $p = 0.004$), but not with any remaining cognitive score. BDI-II did not correlate with any cognitive scores.

In MSA group, BDI-II score correlated with ADL (rho = −0.477, $p = 0.002$) and IADL (rho = −0.445, $p = 0.004$) but not with any remaining cognitive score. AES score correlated with poorer score on phonological fluency task (rho = −0.420, $p = 0.007$).

In PSP group, AES score correlated with score on ADL (rho = −0.491, $p = 0.002$), IADL (rho = −0.623, $p < 0.001$), phonological fluency test (rho = −0.563, $p < 0.001$) and immediate copy of ROCF (rho = −0.523, $p = 0.002$), whereas BDI-II score did not correlate with any cognitive scores.

4.6 Discussion

The present study systematically compared samples of patients with PD, MSA and PSP on a very comprehensive neuropsychological battery to identify cognitive or behavioural differences among Parkinsonian disorders. Since there were significant differences in demographic variables and global cognitive status among the three groups, we performed a comparison on cognitive domain scores achieved by three subgroups of MSA, PD, PSP matched for demographic features and global cognitive functioning (i.e., MoCA score) to control for these potential bias. This procedure revealed significant differences among the three groups on cognitive tests exploring executive functions (i.e., phonological fluency test, TMT-B, and Stroop test) and linguistic functions. The group of patients with PSP was more impaired than the PD and MSA groups on cognitive tests assessing executive functions. On the other hand, the group of patients with MSA obtained similar cognitive performance to the PD group. As to behavioural symptoms, the prevalence of pure apathy (i.e., without co-occurrence of dementia and depression) was higher in patients with PSP (45%) than in patients with MSA (15%) or PD (10%). In the PSP group, apathy and depression were more severe than in the PD group, while apathy (but not depression) were more severe in the PSP group as compared to the MSA group. In patients with PD, symptoms of depression and apathy were less severe than in the MSA group.

Our results that PSP patients are more impaired than PD and MSA patients in some specific executive functions such as cognitive flexibility, set shifting and inhibitory control indicated a marked dysexecutive syndrome in PSP patients when compared to PD or MSA patients, consistently with previous studies [8,9,10]. In particular, in PSP, both spatial planning and set shifting were the most damaged executive functions. Since poor performances on both spatial planning and set shifting tests have been reported as a consequence of a damage of prefrontal cortex in neurodegenerative diseases, our findings support the notion that a consistent group of PSP presents prominent frontal deficits [35]. As a new observation, although the cognitive differences between PD and MSA were statistically not significant, we found that even MSA patients revealed a more marked impairment in executive functions when compared to PD patients supporting the idea frontal-executive dysfunction is an integral part of the disease and the most common presentation in

MSA [36]. In particular, in MSA group, spatial planning was the most damaged executive function. This result indicates that deficit of spatial planning is a prominent executive dysfunction in MSA, affecting up to 50% of patients. Taken together, these results indicated that marked frontal cognitive impairment is associated mainly with atypical Parkinsonism and might reflect a prominent subcortical–frontal connection dysfunction [37]. Moreover, the more marked dysexecutive syndrome in PSP patients compared to MSA and PD ones may result from the deafferentation of the prefrontal and premotor areas due to alteration of striato-thalamo-cortical pathway [38].

As regards to memory domain, we found no significant differences between PD and atypical Parkinsonism on tasks assessing long-term memory, a cognitive function mediated mainly by the hippocampus. Although the volume of hippocampus has been found to be more reduced in atypical Parkinsonism compared to PD [39] the absence of a significant difference on long-term memory tests among the patient groups might suggest that long-term memory is equally impaired among PD, MSA and PSP and thus dysfunction in long-term memory does not allow to distinguish several types of basal ganglia pathologies. However, we observed that PSP patients showed poorer performance than PD ones only on verbal learning. To interpret these finding, we should keep in mind that the performance on this cognitive task may be negatively influenced by lapses of attention and working memory which are aspects of a severe dysexecutive syndrome associated with reduced volume of frontal-subcortical gray matter in PSP [40]. Therefore, the difficulties in verbal learning and recall observed in our PSP patients might be due to lapses of attention, deficits in working memory, inability to initiate and maintain a strategic search of stored information. This inability could be related to dysfunctional organizational and temporal aspects of encoding and retrieval mediated by frontal cortex rather than to a loss of stored information. In support of this idea, no difference among the patient groups was found on delayed recall and recognition tests, which assess long-term memory.

As for linguistic abilities, although the differences among the groups on the repetition and comprehension tasks did not reach the statistical significance, PSP obtained lower scores than MSA and PD. However, we found a significant difference among groups on semantic fluency task where the atypical Parkinsonism

(i.e., PSP) was characterized by more severe impairments when compared to PD. The poor performances on semantic fluency task might be the consequence of speech disorders, such as dysarthria, which are common clinical features of atypical Parkinsonism [41]. Previous evidence of selective impairments of action-verb naming and comprehension in PSP lent to hypothesizing that such linguistic deficits could be due to semantic deficits affecting the conceptual category of actions and could reflect dysfunctions of neural systems in posterior frontal cortical areas critical for processing the conceptual category of actions [42]. Therefore, since we employed comprehensive tests consisting of complex sentences characterized mainly by action verbs, our finding seems to support partially that these deficits in PSP reflect a dysfunctional processing of conceptual category of actions. As for PD patients, although we found a low percentage of patients with impaired performance on linguistic tasks according to Italian normative values (see Table 3), previous evidence demonstrated that PD patients may show impaired performance on tasks assessing naming of verbs [43] and that such impairment in naming verbs may improve after deep brain stimulation of the subthalamic nucleus [44].

As for the behavioural domain, apathy was more severe in PSP than in MSA and PD, confirming the pervasiveness of apathy in PSP [11, 45]. Moreover, the prevalence of pure apathy (i.e., without co-occurrence of dementia and depression) was higher in patients with PSP (45%) than in patients with MSA (15%) or PD (10%). Co-occurrence of apathy and depression was frequent in patients with MSA and PSP.

Correlational analysis, performed in each whole patients group, showed a significant association between apathy and poor performance on frontal tasks in both atypical Parkinsonism and PD patients supporting the frontal origin of apathy [46, 47]. The results of relationship between apathy and poorer scores on executive tests in PD group supported the idea that apathy and executive dysfunctions are both epiphenomena of dysexecutive syndrome related to damaged fronto-subcortical circuitries (see recent meta-analysis [48] and Fig. 4).

Our finding that apathy score and not the depression score significantly correlated with cognitive performance in PSP and in PD evidenced that apathy rather than depression negatively influences cognitive functions in basal ganglia disorders [49]

and that apathy and depression are two distinct syndromes [50]. Moreover, our findings support the idea that apathy and cognitive dysfunction in PSP are the consequence of degeneration in shared prefrontal areas or of dysfunction of shared frontal–subcortical connections [51, 52] and are in line with recent studies showing that frontal atrophy in volumetric MRI studies correlates with behavioural changes in PSP [53]. Even in MSA, apathy rather than depression was associated moderately with poorer performance on phonological fluency tasks. The results might suggest the idea that even in MSA apathy and cognitive dysfunctions are non-motor symptoms induced by focal lesions in the basal ganglia, particularly the caudate, which is engaged in controlling affective aspects of behaviour and is characterized by major neuronal loss in MSA [54].

Our finding that motor symptoms were associated with depression in MSA [55] and apathy in PSP, respectively, might suggest that neurodegenerative processes may progress in the two diseases impacting distinct subcortical and cortical regions. Finally, we found a significant association between the severity of motor symptoms and reduced functional autonomy only in MSA and PSP [56] indicating that motor symptoms drastically reduce patients' autonomy in atypical Parkinsonism rather than in PD.

The present study is characterized by some limitations. First, we did not include healthy control subjects to verify whether cognitive impairments were specific to Parkinsonian syndromes; however, we identified subjects who achieved pathological scores with respect to Italian normative data and provided the percentage of subjects with pathological scores within each patient group. A second limitation of the study might be the unbalanced distribution of the number of cognitive tests in each cognitive domain; in particular, we used many cognitive tests to evaluate the executive domain. However, it allowed us to investigate different types of executive functions such as set shifting, inhibition, cognitive flexibility, spatial organization and planning (for review on executive functions: Diamond [57]). However, another methodological limitation of the study might be the fact that assessment of executive functions did not include any task of problem-solving. Finally, we preferred to apply the National Institute for Neurodegenerative Diseases PSP diagnostic criteria rather than the new Movement Disorders Society

(MDS)-proposed diagnostic criteria for PSP [58] since the MDS criteria have just been released and never applied to any prospectically recruited PSP cohort.

In conclusion, the present study confirms the pervasiveness of cognitive deficits, mainly executive dysfunctions, apathy and depressive symptoms in PSP. Difficulties in set shifting, inhibitory control and cognitive flexibility (i.e., reduced performance on Stroop test, TMT:B and phonological fluency task, respectively; see Table 3) characterized MSA group rather than PD group. The results indirectly indicated the pivotal role of altered basal ganglia and corresponding frontal deafferentation in the occurrence and maintenance of the cognitive and behavioural disturbances.

Table 1 Demographic, clinical, neuropsychological comparisons between atypical Parkinsonism and Parkinson's disease

Parameters	**PD (*n* = 55)**	**MSA (*n* = 44)**	**PSP (*n* = 42)**	**Kruskal–Wallis test**	***P***
Age	66.1 ± 9.7	61.1 ± 8.3	71.2 ± 5.7	28.043	< **0.001**
Education	11.4 ± 4.7	10.5 ± 4.7	8.5 ± 4.7	9.356	**0.009**
Disease duration	5.2 ± 3.6	5.6 ± 3.1	4.7 ± 2.9	2.622	0.270
ADL	5.3 ± 1.2	4 ± 2.1	2.9 ± 1.9	34.663	< **0.001**
IADL	5.7 ± 2.1	4.1 ± 2.2	3 ± 2.4	27.948	< **0.001**
MoCA total score	22.1 ± 3.7*	21.04 ± 4	17.8 ± 5.1	14.516	**0.001**

1. Statistically significant differences are indicated in bold
2. PD, Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; ADL, activities of daily living; IADL, instrumental activities of daily living; MoCA, Montreal Cognitive Assessment
3. *Significant difference between PSP and PD

Table 2 Demographic, clinical, neuropsychological comparisons between Atypical Parkinsonism and Parkinson's Disease (matched for age, education, global cognitive functioning)

Parameters	PD ($n = 20$)	MSA ($n = 20$)	PSP ($n = 20$)	Kruskal–Wallis test	*P*
Age	68.3 ± 3.7	65.9 ± 5.9	67.4 ± 4.1	1.626	0.444
Education	11.3 ± 4.6	10.4 ± 5.4	9.1 ± 4.5	2.701	0.259
Disease duration	5.2 ± 3.6	5.6 ± 3.1	4.7 ± 2.9	1.087	0.581
ADL	5.3 ± 1.2*	4 ± 2.1	2.9 ± 1.9	14.699	**0.001**
IADL	5.7 ± 2.1	4.1 ± 2.2	3 ± 2.4	3.233	0.199
MoCA total score	22.2 ± 1.6	20.5 ± 3.5	20.1 ± 3.6	3.379	0.185
Memory domain					
RAVLT-immediate recall	32.1 ± 10.2*	32.6 ± 13.9	22.4 ± 6.1	13.372	**0.001**
RAVLT-delayed recall	6.8 ± 3.2	6.6 ± 3.2	4.2 ± 1.7	11.530	0.003
RAVLT-recognition	12.8 ± 2.4	12.3 ± 3.8	12.3 ± 2.6	0.812	0.666
Visuospatial functions					
CAT	11.1 ± 1.2*	10.8 ± 1.9	9.1 ± 1.7	11.909	0.003
BJLOT	19.2 ± 6.5	15.8 ± 8.8	13.3 ± 6.2	5.632	0.060
Executive functions					
Phon-fluency test	29.4 ± 12.2*	19.4 ± 11.4	11.7 ± 7.7	19.616	< **0.001**
CDT	9.1 ± 1.8	8.4 ± 2	7.7 ± 2.4	4.335	0.114
ROCF-immediate copy	29.9 ± 6.9*	27.6 ± 6.1	19.5 ± 10.1	13.042	**0.001**
ROCF-delayed copy	13.5 ± 5.5	12.8 ± 6.1	11.4 ± 5.7	2.089	0.352
TMT:B	162.5 ± 81.1*	199.2 ± 100.4#	406.8 ± 239.3	18.793	< **0.001**
TMT:B-A	97.4 ± 69.4*	121.5 ± 77.8#	258.7 ± 138.3	18.117	< **0.001**
Stroop time	31.6 ± 41.5*	21.4 ± 20.8#	47.4 ± 24.4	12.267	**0.002**
Stroop errors	3.2 ± 6.7	11.4 ± 12.1	7.6 ± 9.7	7.152	0.028
Language domain					
Semantic fluency test	33.1 ± 8.7*	27.4 ± 10.1	20.2 ± 10.5	15.192	**0.001**
ENPA-word repetition	9.1 ± 1.2	8.3 ± 2.1	8.6 ± 1.4	1.558	0.459
ENPA-non word repetition	3.6 ± 1.4	3.7 ± 1.2	2.7 ± 1.6	4.578	0.101
ENPA-sentences repetition	2.9 ± 0.3	2.6 ± 0.5	2.6 ± 0.6	4.172	0.124
ENPA—auditory comprehension of single words	13.3 ± 1	13.1 ± 1.1	12.5 ± 1.6	2.525	0.283
ENPA—visual comprehension of single words	13.5 ± 0.8	12.3 ± 1.9	12 ± 2.1	6.618	0.037

Behavioural domain					
BDI-II	8.5 ± 6.6*°	15.3 ± 8.1	18.7 ± 11.4	51.985	< **0.001**
AES	31.9 ± 7.1*°	35.1 ± 8#	45.1 ± 13.3	17.878	< **0.001**

1. Statistically significant differences are indicated in bold
2. PD, Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; ADL, activities of daily living; IADL, instrumental activities of daily living; MoCA, Montreal Cognitive Assessment; RAVLT, Rey's auditory 15-word learning test; BSRT, Babcock Story Recall Test; CAT, constructional apraxia task; BJLOT, Benton Judgment of Lines Orientation Task; Phon-Fluency, phonological fluency; CDT, Clock Drawing Test; ROCF, Rey–Osterrieth Complex Figure Test; TMT, Trail Making Test; ENPA, Esame Neuropsicologico per l'Afasia; BDI-II, Beck Depression Inventory-II; AES, Apathy Evaluation Scale
3. *Significant difference between PSP and PD
4. #Significant difference between PSP and MSA
5. °Significant difference between MSA and PD

Table 3 Percentage of patients with impaired/normal cognitive performance (according to Italian normative values) within each group; percentage of patients with impaired performance (according to Italian normative values) between patients groups; percentage of patients with below/above cut-off score on depression and apathy scales within each group and between patients groups

Ters	**PD**	**MSA**	**PSP**	***F***	***P***
Memory domain					
RAVLT-immediate recall					
I/N performance within group (%)	30/70	35/65	65/35	4.906	0.027
Patients with impaired performance between groups (%)	23.1%	26.9%	50%		
RAVLT-delayed recall					
I/N performance within group (%)	20/80	25/75	20/80	0.193	0.908
Patients with impaired performance between groups (%)	30.8%	38.5%	30.8%		
Visuospatial functions					
CAT					
I/N performance within group (%)	0/100	10/90	42.1/57.9	11.243	0.001
Patients with impaired performance between groups (%)	0%	20%	80%		
BJLOT					
I/N performance within group (%)	23.5/76.5	40/60	52.9/47.1	3.037	0.081
Patients with impaired performance between groups (%)	19%	38.1%	42.9%		

Executive functions					
Phon-fluency					
I/N performance within group (%)	5/95	36.8/63.2	70/30	17.762	< 0.001
Patients with impaired performance between groups (%)	4.5%	31.8%	63.6%		
CDT					
I/N performance within group (%)	6.7/93.3	7.7/92.3	22.2/77.8	1.789	0.181
Patients with impaired performance between groups (%)	16.7%	16.7%	66.7%		
ROCF-immediate copy					
I/N performance within group (%)	25/75	55/45	72.2/27.8	8.395	0.004
Patients with impaired performance between groups (%)	17.2%	37.9%	44.8%		
ROCF-delayed copy					
I/N performance within group (%)	20/80	10/90	11.1/88.9	0.648	0.421
Patients with impaired performance between groups (%)	50%	25%	25%		
TMT:B					
I/N performance within group (%)	5.3/94.7	10/90	47.4/52.6	10.087	0.001
Patients with impaired performance between groups (%)	8.3%	16.7%	75%		
TMT:B-A					
I/N performance within group (%)	10.5/89.5	10/90	47.4/52.6	7.287	0.007
Patients with impaired performance between groups (%)	15.4%	15.4%	69.2%		
Stroop time					
I/N performance within group (%)	5/95	15/85	50/50	10.634	0.001
Patients with impaired performance between groups (%)	7.7%	23.1%	69.2%		
Stroop errors					
I/N performance within group (%)	15/85	45/55	38.9/61.1	4.531	0.104
Patients with impaired performance between	15.8%	47.4%	36.8%		

groups (%)					
Language domain					
Semantic fluency test					
I/N performance within group (%)	10/90	21.1/78.9	60/40	11.592	0.001
Patients with impaired performance between groups (%)	11.1%	22.2%	66.7%		
ENPA-word repetition					
I/N performance within group (%)	26.3/73.7	35/65	37.5/62.5	0.503	0.478
Patients with impaired performance between groups (%)	27.8%	38.9%	33.3%		
ENPA non-word repetition					
I/N performance within group (%)	5.3/94.7	5/95	25/75	3.210	0.073
Patients with impaired performance between groups (%)	16.7%	16.7%	66.7%		
ENPA-sentence repetition					
I/N performance within group (%)	10.5/89.5	35/65	37.5/62.5	3.299	0.069
Patients with impaired performance between groups (%)	13.3%	46.7%	40%		
ENPA—auditory comprehension of single words task					
I/N performance within group (%)	0/100	10.5/89.5	17.6/82.4	3.348	0.067
Patients with impaired performance between groups (%)	0%	40%	60%		
ENPA—visual comprehension of single word task					
I/N performance within group (%)	7.7/92.3	20/80	38.9/61.1	3.978	0.046
Patients with impaired performance between groups (%)	10%	20%	70%		
Behavioural domain					
BDI-II					
Percentage of patients with score below/above cut-off within group	0/100	52.6/47.4	52.9/47.1	10.760	0.001
Depressed patients between groups	0%	52.6%	52.9%		
AES					
Percentage of patients with score below/above cut-off	11.8/88.2	50/50	80/20	16.742	< 0.001

within group					
Apathetic patients between groups	7.1%	35.7%	57.1%		

PD, Parkinson's disease; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; ADL, activities of daily living; IADL, instrumental activities of daily living; MoCA, Montreal Cognitive Assessment; RAVLT, Rey's auditory 15-word learning test; BSRT, Babcock Story Recall Test; CAT, Constructional Apraxia Task; BJLOT, Benton Judgment of Lines Orientation Task; Phon-Fluency, Phonological Fluency; CDT, clock drawing test; ROCF, Rey–Osterrieth Complex Figure Test; TMT, Trail Making Test; ENPA, Esame Neuropsicologico per l'Afasia; BDI-II, Beck Depression Inventory-II; AES, Apathy Evaluation Scale; I, impaired; N, normal

Fig. 1 Pie charts represent the percentage of impaired cognitive domains for MSA, PSP and PD groups

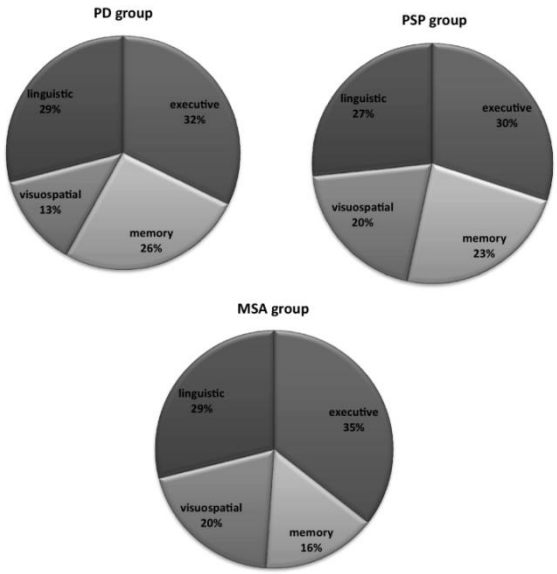


Fig. 2 Pie charts report the percentage of impaired specific executive functions for MSA, PSP and PD groups

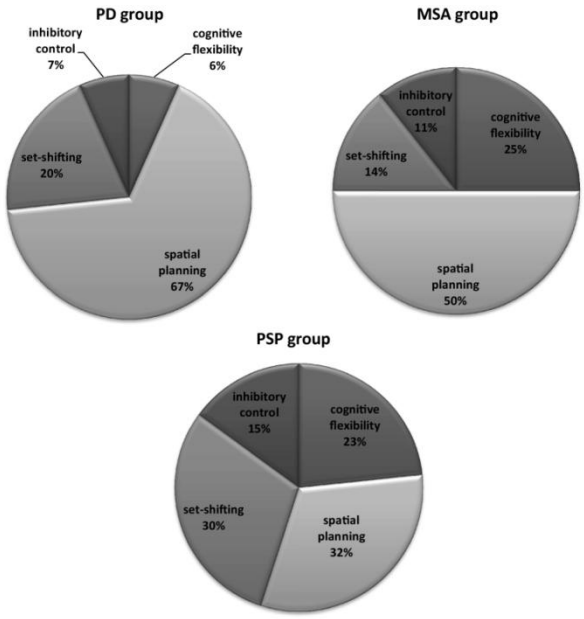


Fig. 3 Pie charts report the percentage of patients with pure apathy, patients with pure depression, patients with apathy and depression, patients without apathy and depression for MSA, PSP and PD groups.

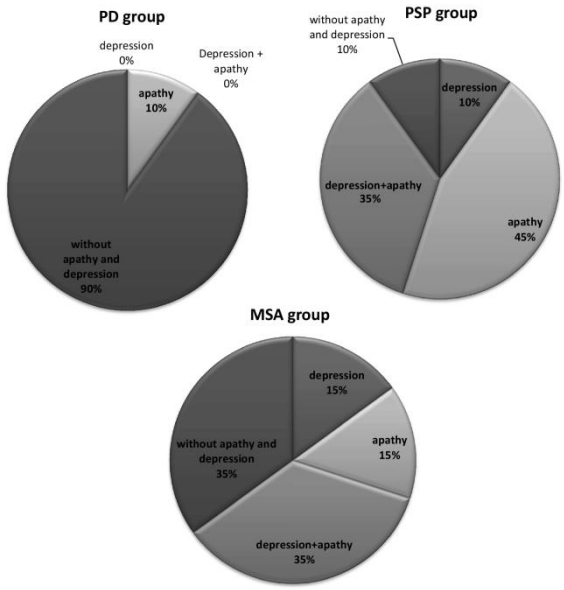
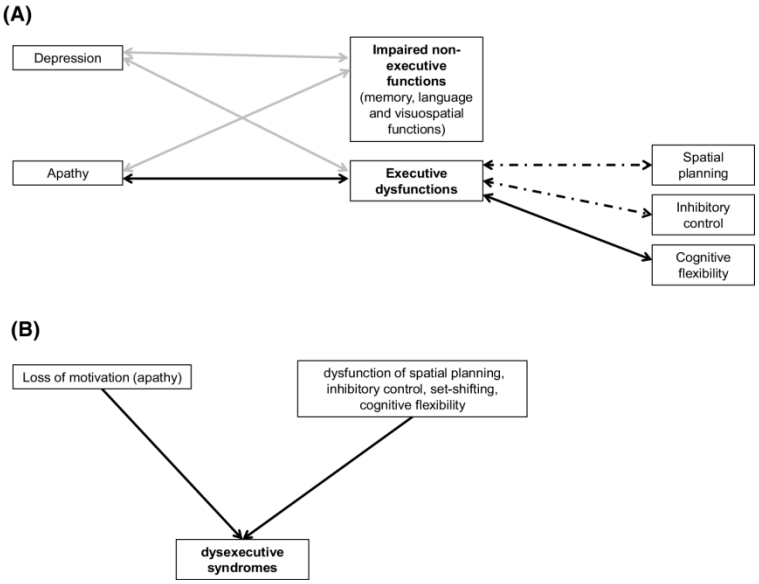


Fig. 4 Model of the relationship between apathy, depression and different cognitive dysfunctions in patients with MSA, PD and PSP



The figure shows that, despite the type of disease, apathy but not depression was related to executive dysfunctions. In part A, the correlational results of relationship between apathy/depression and cognitive domains were shown. Gray line indicates no correlation in MSA, PD and PSP groups; black line indicates correlation in MSA, PD and PSP groups; black broken line indicates correlation in PD group or in PSP group. In part B, apathy and executive dysfunctions are reported as connected with dysexecutive syndrome and considered as epiphenomena of the dysexecutive syndromes despite the type of diseas.

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Chapter III

PROGRESSIVE SUPRANUCLEAR PALSY

1. Clinical use of SAND battery to evaluate language in patients with Progressive Supranuclear Palsy

Published in *PLoS One* 2019;14(10):e0223621.

1.1 Abstract

Background: Progressive Supranuclear Palsy (PSP) patients present language disturbances in tasks like naming, repetition, reading, word comprehension and semantic association compared to Parkinson's disease (PD) and healthy controls (HC).

Objective: In the present study we sought to validate a Screening for Aphasia in NeuroDegeneration (SAND) battery version specifically tailored on PSP patients and to describe language impairment in relation to PSP disease phenotype and cognitive status.

Methods and results: Fifty-one PSP [23 with Richardson's syndrome (PSP-RS), 10 with predominant parkinsonism (PSP-P) and 18 with the other variant syndromes of PSP (vPSP)], 28 PD and 30 HC were enrolled in the present study. By excluding the tasks with poor acceptability (i.e., writing and picture description tasks) and increasing the items related to the remaining tasks, we showed that the PSP-tailored SAND Global Score is an acceptable, consistent and reliable tool to screen language disturbances in PSP. However, we failed to detect major

differences in language involvement according to disease phenotype. Differently, we showed that patients with dementia present worse language performances. **Conclusions:** Taking into account specific disease features, the combination of the SAND subscores included in the PSP-tailored SAND better represents language abilities in PSP. Furthermore, we showed that language disturbances feature PSP patients irrespective of disease phenotype, but parallels the deterioration of the global cognitive function.

1.2 Introduction

Progressive Supranuclear Palsy (PSP) is a rare, rapidly progressive neurodegenerative disease characterized by postural instability and supranuclear vertical gaze palsy as well as by cognitive and behavioral symptoms [1]. According to the clinical diagnostic criteria proposed by the Movement Disorder Society (MDS)[2], language impairment is part of the complex spectrum of disturbances affecting patients with PSP. As such, PSP with predominant speech-language disorder (PSP-SL) is recognized as an independent clinical phenotype reaching the diagnostic level of possibility associated with a probable 4R-tauopathy pathology (i.e., either PSP or Cortico-basal Degeneration)[2]. However, evidence suggests that a wide spectrum of language deficits characterize also the remaining PSP phenotypes, including Richardson's syndrome (PSP-RS). Recently, Burrell et al. reported that patients with PSP-RS present specific language deficits similarly to those affected by Primary Progressive Aphasia (PPA)[3]. To date, there is scant of evidence on the language profile of PSP patients diagnosed according to MDS clinical criteria [4].

The Screening for Aphasia in NeuroDegeneration (SAND) battery is a brief validated tool to detect language impairment in patients affected by neurodegenerative diseases through the assessment of different components of language [5,6]. The SAND battery is proved to detect subtle language impairment in PSP phenotypes other than PSP-SL, such as lexical-semantic level disturbances in comparison with Parkinson's disease (PD) and healthy controls (HC)[4]. However, peculiar PSP clinical features may prevent a proper application of specific language tasks included in the SAND battery.

In the present study we aimed to validate a version of the SAND battery specifically tailored for PSP and to use it to describe language performances in PSP according to disease phenotype and cognitive status.

1.3 Methods

Patients

Between November 2015 and December 2018, consecutive cases of suspected PSP referred to the Center for Neurodegenerative Diseases of the University of Salerno were proposed a dedicated set of assessments including a clinical interview, a motor evaluation, extensive cognitive and behavioral testing, language evaluation and brain MRI.

For each enrolled patient the MDS proposed diagnostic flowchart was applied by two specialists for movement disorders who defined the PSP phenotypes [23 PSP-RS, 10 PSP with predominant parkinsonism (PSP-P), 9 PSP with predominant corticobasal syndrome (PSP-CBS), 4 PSP with progressive gait freezing (PSP-PGF) and 5 PSP with predominant frontal presentation (PSP-F)] according to the predominant clinical features and expressed the degree of diagnostic certainty [2,7,8]. Diagnosis as well as phenotypic attribution was verified for all patients during at least one subsequent visit. As PSP-CBS, PSP-PGF and PSP-F included a limited number of patients, those subtypes were grouped together as the other variant syndrome of PSP (vPSP = 18).

In addition, two groups of age-matched HC (N = 30) and PD (N = 28) patients were also enrolled for the present study. Exclusion criteria for enrollment of PD patients were diagnosis of dementia in accordance with MDS criteria and H&Y in on state>3. Exclusion criteria for enrollment of HC were the presence of any neurological or psychiatric conditions.

The project was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. As such, the study was approved by the local Ethics Committee (Campania Sud) and each subject was included upon signature of the informed consent form.

Clinical and cognitive evaluations

Severity of the disease was evaluated with the PSP rating scale (PSP-rs)[9].

Cognitive abilities were screened with the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Memory domain was investigated with the immediate and delayed recall scores of the Rey auditory verbal learning test (15-RAWLT) and the Rey figure recall test. Attention-executive domain was explored through the Trail Making Test (TMT), the short version of the Stroop Interference Test, the Clock design test (CDT) and the Rey figure copying test (RCF). Visuo-spatial functions were tested with the constructional apraxia test and Benton orientation line test (BJLO) [10]. Language was explored with two sub-tests from the Neuropsychological Examination of Aphasia battery (ENPA), the non-word repetition test and the auditory comprehension test of sentences.

Functional autonomy was evaluated with the Instrumental Activities of Daily Life (IADL), while depression and apathy with the Beck Depression Inventory II (BDI-II) and Apathy Evaluation Scale (AES), respectively [11,12].

Using the z scores computed with the scores from the HC group, each PSP patient was classified as having PSP with normal cognition (PSP-NC = 4), PSP with mild cognitive impairment (MCI) single domain (PSP-MCIsd = 9), PSP with MCI-multiple domain (PSP-MCImd = 24) and PSP with dementia (PSP-D = 12) [13,14].

Due to the lack of specific MCI criteria for PSP, MDS MCI criteria for Parkinson's disease were applied [14]. Patients presenting any type of cognitive/behavioral decline associated with impairment of IADL were considered as affected by dementia (PSP-D), according to Statistical Diagnostic Manual of Psychiatry–5th Edition (DSM-5).

Language testing

Language was evaluated with the SAND battery [5,6]. The SAND Global Score including the 23 task-related scores was computed according with a previously described process [5]. In brief, the SAND global score is a frequency count of the pathologically impaired sub-scores with higher scores indicating more severe impairment. However, SAND Global score acceptability and consistency in PSP

patients was suboptimal due to a high proportion of missing data in the writing and connected speech tasks (S1 Appendix). Therefore, following the three steps process as noted in S1 Appendix, a PSP-tailored SAND Global Score was created, reducing the impact of the writing and picture description subscores and expanding the relevance of the remaining tasks subscores (Table 1). The PSP-tailored SAND Global Score ranges from 0 to 19, with higher scores indicating greater impairment. (S1 Appendix).

1.4 Statistical analysis

After checking for normality distribution with the Kolmogoroy-Smirnov test, differences in variables between groups were computed with χ^2 or the Kruskal-Wallis tests as appropriate. Pairwise comparisons were performed with Mann-Whitney's U test.

Acceptability and internal consistency were explored for both the SAND Global Score and the PSP-tailored SAND Global Score. Acceptability was considered appropriate for each Global Score if ≤15% of the respondents totalized the lowest and highest possible scores (floor and ceiling effect) and for each Global Score item if there were ≤5% of missing values. Moreover, skewness of Global Scores (limits, -1 to +1) was determined [15].

Internal consistency was evaluated by means of Cronbach's alpha [16]. A value≥0.70 was considered as acceptable [17]. Since the SAND Global Score showed suboptimal acceptability and consistency in PSP patients (see Results and S1 Appendix), subsequent analyses were performed only for the PSP-tailored SAND Global Score.

Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation for PSP-tailored SAND Global Score (standard, ≥0.40 [18]).

Construct validity was explored with non-parametric Spearman's correlation between the PSP-tailored SAND Global Score and other language testing as well as with cognitive and behavioral testing. Correlations were considered strong with coefficient>0.70 and moderate with coefficient between 0.30 and 0.70. SAND

scores were not expected to correlate with memory and behavioral testing, while were expected to correlate with other language and cognitive testing.

ROC analysis was performed for the PSP-tailored SAND Global Score to identify the optimal cut off to detect language impairment in PSP patients compared to both PD and HC. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and diagnostic accuracy in comparison to clinical diagnosis were assessed at the best threshold for classification.

Post-hoc Bonferroni test was used to correct for multiple comparisons. Statistical analysis was performed with SPSS (Version 23).

1.5 Results

Sixty-two PSP patients were considered for the present study, but 11 were excluded according to specific inclusion/exclusion criteria detailed above. In detail, in six patients the clinical diagnosis of PSP was not confirmed in subsequent visits, four patients were not able to complete the SAND battery and one patient presented PSP-SL. The final cohort, thus, included 51 PSP patients (Table 2). According to MDS degrees of diagnostic certainty, all PSP patients had a diagnosis of probability (ie, presenting either a clear limitation of the range or decreased velocity and amplitude of vertical gaze plus other features) but those-by definition-with PSP-CBS [2]. As such, although PSP-CBS is featured by either a clear limitation of the range or decreased velocity and amplitude of vertical gaze, the presence of a corticobasal syndrome still raises the differential diagnosis with Corticobasal disease. Since no in vivo biomarkers are available differentiating PSP from Corticobasal disease, thus, PSP-CBS remains a diagnosis of possibility [2]. PSP patients presented worse performances on both the SAND Global Score and the PSP-tailored SAND Global Score compared with both PD and HC, reflecting, thus, worse language abilities (Table 2).

Validation phase

Although no floor effect was observed, a tendency to ceiling effect was reported for the SAND Global score (0.2% of participants obtained the lowest possible score and 15.2% the highest possible score). Skewness was 0.527. However,

missing values were 30.7% and 13.3% in writing and picture description tasks, respectively, compared to 0% in the remaining tasks (S1 Appendix). Cronbach's alpha for the SAND Global score was 0.405 and, thus, it was considered suboptimal for internal consistency [16]. Reducing the items related to the tasks with suboptimal acceptability (i.e., writing and picture description tasks) and increasing the items related to the remaining tasks significantly improved Cronbach's alpha from 0.405 to 0.887 indicating high-level internal consistency (S1 Appendix). By removing additional items, no further improvement of Cronbach's alpha was detected. Therefore, the 19-items PSP-tailored SAND Global Score was conceived. Neither ceiling or floor effect were observed for the PSP-tailored SAND Global Score (lowest possible score = 0, 4.8% of the participants; highest possible score = 17, 0.9% of the participants). Skewness of the PSP-tailored SAND Global Score was 0.965. All the PSP-tailored SAND Global Score items presented excellent acceptability as there were no missing data and 100% of data were computable. Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation (standard, ≥0.40).

Spearman's correlation confirmed convergent validity of the single tasks included in the PSP-tailored SAND Global Score, demonstrating significant moderate correlations with other language testing (Table 3). As for the other cognitive tests, moderate correlation was demonstrated with measures of global cognition as the MoCA, but not with the MMSE, as well as with tests exploring visuospatial and attention-executive domains. No correlation was shown with tests exploring memory domain or behavioral scales, while moderate correlation emerged with disease severity as assessed with the PSP-rs (S1 Appendix).

Determining the optimal cut off of the PSP-tailored SAND Global Score

ROC analysis was used to assess the discriminatory power of the PSP-tailored SAND Global Score in identifying language impairment in PSP compared to both HC and PD.

As for the comparison with HC, the ROC analysis showed an 87.6% discriminatory power [95% confidence interval (CI), 80.1–95.2%]. The determined optimal cut off was 3 showing 74.5% sensitivity, 80% specificity, 86.4% positive predictive value

(PPV), 64.9% negative predictive value (NPV) and 76.5% diagnostic accuracy (S1 Appendix).

As for the comparison with PD, the ROC analysis showed an 80% discriminatory power (95%CI, 69.7–91.2%). The determined optimal cut off was 3 showing 74.5% sensitivity, 71.4% specificity, 82.6% PPV, 60.6% NPV and 73.4% diagnostic accuracy (S1 Appendix).

PSP-tailored SAND and disease features

SAND task subscores in PSP, PD and HC are shown in S1 Appendix. PSP patients reported worse outcome in all SAND task subscores as well as in the PSP-tailored SAND Global Score compared to both PD and HC.

No differences were detected in the PSP-tailored SAND Global Score among patients with different disease phenotypes (Table 4).

PSP-D showed worse PSP-tailored SAND Global Score compared to both PSP-MCIsd and PSP-NC. However results were not significant when correcting for multiple comparisons (Table 5).

1.6 Discussion

The present study showed that the PSP-tailored SAND battery is acceptable, reliable, and easily applicable to PSP patients. By removing subscores with high proportion of missing values and expanding subscores of the remaining tasks, we used the best combination of SAND tasks to screen language ability in PSP leading to a significant improvement in consistency and acceptability as compared to the original SAND Global Score [5,15]. As a matter of fact, differently from patients with PPA, PSP patients disclose peculiar clinical features possibly impacting performances on specific language tasks. Specifically, ocular movement abnormalities may hamper the visual exploration of the picture description and possibly impact the performances of connected speech task for non linguistic reasons. Similarly, the writing task can be affected by both apraxia and bradykinesia. The combination of SAND tasks included in the PSP-tailored SAND Global Score overcome such limits showing high acceptability since data were computable for 100% and the percentage of missing values was 0% for all items. The excellent acceptability by PSP patients is also supported by the absence of both ceiling and floor effects as well as by the optimal skewness.

Furthermore, the internal consistency of the PSP-tailored SAND battery is high and acceptable (Cronbach's alpha = 0.887; item—total score correlation≥0.40 for all items) suggesting a coherent representation of all the language functions screened. As for convergent construct validity, each task of the PSP-tailored SAND battery showed significant moderate correlation values with other corresponding language testing. Furthermore, the PSP-tailored SAND Global Score showed moderate correlation with measures of global cognition as well as with cognitive tests exploring attention-executive and visuospatial domains. The positive association with the PSP-rs suggests a correlation between language abilities and severity of disease. No association was shown with behavioral assessments suggesting divergent validity between language function and apathy and depression burden in PSP patients.

As for the discriminatory power of the PSP-tailored SAND Global Score, the optimal cut off of 3 demonstrated an adequate sensitivity and specificity profile in identifying language impairment compared to both PD and HC. This is the first study showing a cut off for a language battery differentiating PSP from PD and HC. Previous evidence showed the SAND cut off of 5 was able in differentiating PPA from patients affected by movement disorders (PD and PSP)[5].

Confirming previous findings on a smaller cohort of patients [6], PSP patients other than PSP-SL present language disturbances when compared to both PD and HC age-matched groups (S1 Appendix).

As for language evaluation according to disease phenotype, we failed to detect significant differences suggesting language is globally involved in PSP irrespective of the specific phenotype. Confirming previous findings [13], available clinical and cognitive assessments hardly capture clinical differences among MDS PSP phenotypes.

As for the relationship between language and cognitive status, we detected a trend for worse language performances in PSP-D compared to both PSP-MCIsd and PSP-NC suggesting that language deficit may be related to the extent of impairment of the cognitive networks.

Our study has several strenghts. Firstly, the large sample size of early PSP patients enrolled (median disease duration = 4 years) representing the different phenotypes of the disease as well as the inclusion of age-matched groups of PD and HC

subjects. Secondly, all included patients underwent a thorough evaluation with an extensive battery of clinical assessments by a specialist for movement disorder in a third level center and were diagnosed according to recent MDS criteria [2]. Finally, we are the first to propose an evaluation of language abilities in PSP taking into account specific disease features possibly impacting on language evaluation.

On the other hand, we acknowledge the lack of pathological confirmation, still the gold standard for PSP diagnosis, is a major limitation of our study. Another limitation of our study is the lack of cross-validation procedures for the ROC analysis which can lead to an under- or over-estimation of the PSP-tailored SAND Global score cut-off to discriminate between PSP and PD and HC subjects. However, as ocular disturbances and postural instability remain the cardinal features of PSP, language testing, as the SAND battery, would not represent a diagnostic testing for such condition. Finally, we missed to evaluate the motor speech component with appropriate instruments and despite our attention to clean the battery from items affected by intrinsic characteristics of PSP, the relationship between language tests and hearing still remains open. Extensive evidence supports auditory dysfunction as an additional nonmotor feature of PD, but there are no studies investigating hearing in PSP patients [20].

In conclusion, the combination of the SAND subscores included in the PSP-tailored SAND Global Score represents an acceptable and reliable tool to screen for language abilities in PSP. Furthermore, we showed that language disturbances feature PSP patients irrespective of disease phenotype, but may parallel the deterioration of the global cognitive function.

Table 1PSP-tailored SAND Global score (from 0 to 19).

A)Naming
1)Total
2)Living
3)Non-living
B)Sentence comprehension
C)Single word comprehension
1)Total
2)Living

3)Non-living
D)Repetition
1)Total
2)Words
3)Non words
E)Sentence repetition
1)Total
2)Predictable
3)Unpredictable
F)Reading
1)Total
2)Words (regular and irregular)
3)Non words
G)Semantic associations
H)Writing
1)Information units
I)Picture description
1)Informative units

Table 2 Demographic and clinical features of enrolled subjects.

	PSP (51)	**PD (28)**	**HC (30)**	**p**
Age, years	71.00 (10.0)	67.00 (8.0)	66.00 (13.5)	0.229
Disease duration, years	4.00 (4.00)	5.00 (6.0)	NA	0.271
Sex, men, n (%)	29 (56.9)	21 (75)	11 (36.7)	0.013
Education, years	9.00 (9.0)	11.5 (8)	8.00 (10.5)	0.347
MMSE	24.00 (6.0)	28.00 (3.0)	27.00 (2.0)	**<0.001**[a,b]
SAND Global Score	6.00 (4.0)	2.00 (2.8)	1.50 (3.0)	**<0.001** [a,b]
PSP-tailored SAND Global Score	8.00 (8.0)	1.00 (4.8)	1.00 (2.0)	**<0.001**[a,b]
PSP-rs	43.50 (23.8)	NA	NA	NA

Data are in median (Interquartile range, IQR), unless otherwise specified.

Significance threshold corrected for multiple comparisons = 0.002; significant differences are highlighted in bold.
Abbreviations:
a: PSP versus HC $p < 0.001$
b: PSP versus PD $p < 0.001$; HC: healthy controls; MMSE: Mini-Mental State Examination; NA: not applicable; PD: Parkinson's disease; PSP: progressive supranuclear palsy; PSP-rs: progressive supranuclear palsy—rating scale; SAND: Screening for Aphasia in NeuroDegeneration.

Table 3 Spearman's correlation between single tasks of the PSP-tailored SAND Global Score and other language tests.

SAND Task	Language tests	Spearman's correlation	p
Naming	CaGi naming [19]	0.523	**0.001**
Word comprehension	Auditory sentence comprehension (ENPA)	0.453	0.003
	Visual sentence comprehension (ENPA)	0.559	**0.002**
Sentence comprehension	Auditory sentence comprehension (ENPA)	0.577	**<0.001**
	Visual sentence comprehension (ENPA)	0.655	**<0.001**
Words/non words repetition	Word repetition (ENPA)	0.600	**<0.001**
	Non-word repetition (ENPA)	0.522	**<0.001**
Sentence repetition	Sentence repetition (ENPA)	0.362	0.045
Reading	Word repetition (ENPA)	0.441	0.004
	Non-word repetition (ENPA)	0.417	0.006
	Auditory sentence comprehension (ENPA)	0.616	**<0.001**
	CaGi naming [19]	0.478	0.004
	Visual sentence comprehension (ENPA)	0.482	0.011
Semantic association	CaGi naming [19]	0.500	0.003
	Auditory sentence comprehension (ENPA)	0.444	0.020
Writing I.U.	**Category fluency**	0.339	0.035
Connected speech I.U.	**Word repetition (ENPA)**	0.459	0.004
	Non-word repetition (ENPA)	0.545	**<0.001**
	CaGi naming [19]	0.626	**<0.001**

Significance threshold corrected for multiple comparisons = 0.002; significant differences are highlighted in bold.
Abbreviations: ENPA = Esame Neuropsicologico dell'Afasia; I.U = Informative Units; PSP = Progressive Supranuclear Palsy; SAND = Screening for Aphasia in NeuroDegeneration.

Table 4PSP-tailored SAND in PSP disease phenotypes.

	Continuous scores				**Impaired scores (%)**			
SAND task	**PSP-RS (23)**	**PSP-P (10)**	**vPSP (18)**	**P**	**PSP-RS (23)**	**PSP-P (10)**	**vPSP (18)**	**p**
Naming								
Total	10 (4.25)	13 (6)	10 (5.25)	0.348	47.8	30	38.9	0.614
Living	6 (3.5)	6 (3)	4 (4)	0.857	34.8	20	33.3	0.685
Non-living	5 (2)	7 (1)	5 (1.75)	0.072	65.2	20	61.1	0.045
Sentence comprehension	6 (3.5)	8 (1)	7 (3)	0.378	50	40	50	0.852
Single word comprehension								
Total	10 (3)	12 (1)	12 (2)	0.047	60.9	10	44.4	0.026
Living	5 (3)	6 (1)	6 (1.5)	0.046	60.9	20	44.4	0.093
Non-living	5 (2)	6 (1)	6 (1)	0.444	39.1	10	16.7	0.119
Repetition								
Total	7 (3.5)	8 (4)	6 (2)	0.331	34.8	50	58.8	0.308
Words	6 (1.5)	6 (1)	5 (2)	0.448	21.7	20	33.3	0.634
Non words	1 (2)	2 (3)	1 (2.5)	0.752	26.1	50	44.4	0.313
Sentence repetion								
Total	3 (2.5)	3 (1)	2 (4)	0.491	43.5	40	61.1	0.436
Predictable	1 (1.5)	1 (1)	1 (2)	0.763	52.2	60	61.1	0.827
Unpredictable	1 (1)	1 (1)	1 (1.5)	0.316	17.4	10	38.9	0.145
Reading								
Total	14 (6.5)	14 (4)	15 (8.5)	0.835	47.8	40	50	0.875
Words	11 (4.5)	10 (4)	11 (5)	0.949	47.8	60	50	0.809
Non words	3 (2)	4 (1)	3 (3)	0.081	43.5	0	38.9	0.043
Semantic associations	2 (1.5)	2 (3)	2 (1)	0.677	13	20	16.7	0.871
Writing								
Information Units	3 (2.5)	4 (1)	2 (4)	0.030	25	0	42.9	0.088
Picture description								
Information Units	4 (2.5)	3 (7)	4 (2)	0.625	42.1	50	38.9	0.869
PSP-tailored SAND Global Score	9 (9.5)	4 (7)	7 (5.5)	0.364	69.6	70	83.3	0.565

Significance threshold corrected for multiple comparisons < 0.001

Table 5 PSP-tailored SAND in PSP according to cognitive status.

	Continuous scores					**Impaired scores (%)**				
SAND task	**PSP-D (12)**	**PSP-MCImd (24)**	**PSP-MCI sd (9)**	**PSP-NC (4)**	**P**	**PSP-D (12)**	**PSP-MCImd (24)**	**PSP-MCIsd (9)**	**PSP-NC (4)**	**p**
Naming										
Total	10 (5)	10 (5)	11.5 (5.25)	14 (0)	0.094	58.3 %	45.8%	22.2%	0%	0.209
Living	5 (2.75)	5 (4)	5 (3.25)	7 (0)	0.303	33.3 %	33.3%	33.3%	0%	0.693
Non-living	5 (3)	5 (1.5)	6.5 (3)	7 (0)	0.065	75%	58.3%	44.4%	0%	0.118
Sentence comprehension	5 (3.5)	7 (3)	7.5 (1.25)	10 (4)	*0.019*[a,c,e,f]	66.7 %	50%	25%	0%	0.055
Single word comprehension										
Total	10 (4)	10 (4)	11.5 (1)	12 (1)	*0.016*[a,c,e,f]	66.7 %	45.8%	22.2%	0%	*0.042*[a,c]
Living	4 (3)	5 (3)	6 (1)	6 (1)	0.056	66.7 %	41.7%	44.4%	0%	0.093
Non-living	5 (2)	5 (2)	6 (0.25)	6 (1)	0.175	41.7 %	25%	11.1%	0%	0.327
Repetition										
Total	7 (3.5)	7 (3)	7.5 (2.75)	7.5 (2)	0.316	50%	50%	22.2%	66.7 %	0.590
Words	6 (2)	5 (2)	6 (1)	6 (2)	*0.021*[d,f]	33.3 %	37.5%	0%	0%	0.119
Non words	1 (2.5)	2 (2)	2 (2.5)	1 (2.5)	0.846	41.7 %	41.7%	22.2%	50%	0.621
Sentence repetion										
Total	3 (3)	3 (2)	2 (2)	6 (0)	0.197	58.3 %	50%	55.6%	0%	0.351
Predictable	1 (1)	1 (2)	1 (0.5)	3 (0)	0.233	66.7 %	62.5%	55.6%	0%	0.192
Unpredictable	1 (1)	1 (1)	1 (1.5)	3 (0)	0.102	41.7 %	16.7%	22.2%	0%	0.304
Reading										
Total	11 (8)	14 (4)	16 (3.25)	15 (0)	0.039[a]	66.7 %	50%	11.1%	25%	*0.047*[a,d]
Words	9 (6.5)	11 (4)	12 (2.25)	11 (0)	0.140	66.7 %	50%	33.3%	25%	0.256
Non words	2 (2.5)	4 (2)	4 (1)	4 (0)	*0.029*[a,c]	58.3 %	29.2%	11.1%	0%	*0.021*[a,c]
Semantic associations	2 (1.5)	2 (1)	2.5 (1.5)	3 (0)	0.355	25%	16.7%	11.1%	0%	0.724
Writing										
Information Units	1 (3)	3 (3)	4 (1.5)	4 (0)	*0.009* [a,b,c]	66.7%	19%	0%	*25%*	*0.012*[a,b]
Picture description										
Information Units	3 (3.5)	4 (3)	4 (4)	3 (0)	0.475	63.6 %	33.3%	28.6%	50%	0.488

	Continuous scores					Impaired scores (%)				
SAND task	**PSP-D (12)**	**PSP-MCImd (24)**	**PSP-MCI sd (9)**	**PSP-NC (4)**	**P**	**PSP-D (12)**	**PSP-MCImd (24)**	**PSP-MCIsd (9)**	**PSP-NC (4)**	**p**
PSP-tailored SAND Global Score	9 (10)	8 (9)	5 (6.5)	3 (0)	*0.024*[a,c]	83.3 %	75%	66.7%	50%	0.603

No significant differences were detected according with the significance threshold corrected for multiple comparisons (< 0.001). However, in Italics are highlighted significant differences detected with the significance threshold set at $p < 0.05$

a = Dementia vs MCI-sd
b = Dementia vs MCI-md
c = Dementia vs NC
d = MCI-sd vs MCI-md
e = MCI- sd vs NC
f = MCI-md vs NC.

Supplementary material

The SAND provides a brief comprehensive language assessment tailored for patients with PPA, including: (1)Picture naming: The subject is asked to name 14 black and white object drawings; (2)Sentence comprehension: The subject is asked to choose which of two pictures matches the meaning of the sentence read by the examiner. The sentences included two short active, two short passive, two coordinates and two embedded structures; (3)Word comprehension: The subject is asked to point at the target among four object pictures in response to a spoken word; (4)Repetition: The subject is asked to repeat words and non-words read by the examiner; (5)Sentence repetition: The subject is asked to repeat the sentences read by the examiner; (6)Reading: The subject is asked to read regular and irregular words and non-words; (7)Semantic association: the subject is asked to point at the two semantically related images out of three; (8)Writing: The subject is asked to describe how to brush their teeth; (9)Picture description task: The subject is asked to describe a complex picture [5,6].

The entire battery is short and can be administered to PSP patients in less than 20 minutes [4]. For each of the 9 subtests a score can be computed. In addition, picture description and written description analysis yields additional subscores, resulting in a total of 23 task-related scores [5,6]. Hence, the SAND Global Score including the 23 task-related scores was computed according with a previously described three steps process: (1)The raw scores were adjusted by adding or subtracting the influence of age, sex, and education and corrected using available normative data [6]; (2)Corrected scores were compared with the corresponding cutoff values obtained from HC; (3)The sum of the twenty-three dichotomous variables (1=pathological, 0=normal) represented the SAND Global Score, with higher scores indicating more severe impairment (SAND global score range:0–23)[5].

SAND Global score (0-23) (Battista 2018)

A)Naming
1)Total
B)Sentence comprehension

C)Single word comprehension
1)Total
D)Repetition
1)Total
E)Sentence repetition
1)Total
F)Reading
1)Total
G)Semantic associations
H)Writing
1)Information units
2)Total words
3)Nouns/total words
4)Verbs/total words
5)sentences
6)Orthographic errors
7)semantic errors
I)Picture description
1)Informative units
2)Number of words
3)Nouns/words
4)Verbs/words
5)Repaired sequences/number of words
6)Sentences
7)Subordinate/sentences
8)Phonological errors/number of words
9)Semantic errors/number of words

SAND Global score acceptability and consistency in PSP patients was suboptimal due to a high proportion of missing data in the writing and connected speech tasks. More than half of PSP patients with missing data refused to complete such tasks because they felt unable to perform the assignments. As for the picture description task, this was likely due to the gaze palsy. While for the writing task, this was likely due to both apraxia and bradykinesia.

Table: Valid and missing data of SAND battery: comparison between the writing and the picture description tasks and all the remaining SAND tasks.

	Writing task	**Picture description task**	**All the remaining SAND tasks**
Valid data	39	45	51
Missing data	12	6	0

$p< 0.001$ for comparison between writing task and all the other SAND tasks
$p< 0.001$ for comparison between picture description task and all the other SAND tasks

Therefore, following the three steps process as noted above, a PSP-tailored SAND Global Score was created, reducing the impact of the writing and picture

description subscores and expanding the relevance of the remaining tasks subscores. The PSP-tailored SAND Global Score ranges from 0 to 19, with higher scores indicating greater impairment.

PSP-tailored SAND Global score (our proposal)
A)Naming
1)Total
2)Living
3)Non-living
B)Sentence comprehension
C)Single word comprehension
1)Total
2)Living
3)Non-living
D)Repetition
1)Total
2)Words
3)Non words
E)Sentence repetition
1)Total
2)Predictable
3)Unpredictable
F)Reading
1)Total
2)Words (regular and irregular)
3)Non words
G)Semantic associations
H)Writing
1)Information units
I)Picture description
1)Informative units

By reducing the items of the picture description and writing tasks and expanding the items of other tasks, acceptability of the SAND battery presented a significant improvement (see Results).

Additional inclusion criteria for the present study were: (a) Italian native speaker status; (b) sufficiently intelligible speech such that the intended target could be determined for the majority of words; (c) intact or corrected auditory and visual functions; (d) disease duration less than 10 years; (e) successful completion of the language testing. Additional exclusion criteria included: (a) Mini-Mental State Examination (MMSE) < 10 [5]; (b) fulfillment of the criteria for PSP-SL [2].

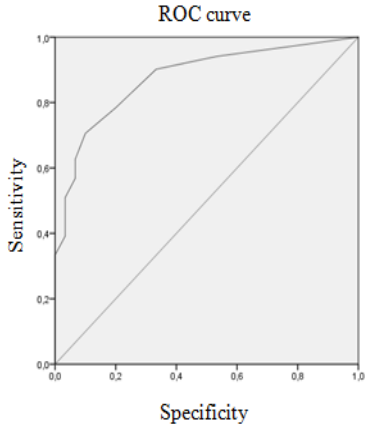
Supplemental Figure. a Summary of the diagnostic accuracy of the SAND battery for the comparison of PSP patients versus HC. **b** ROC curve for the Global Score of the SAND battery to detect patients with language dysfunction evacuate in the sample of PSP patients versus HC. **c** Summary of the diagnostic accuracy of the SAND battery for the comparison of PD patients versus PSP patients. **d** ROC curve for the Global Score of the SAND battery to detect patients with language dysfunction evaluated in the comparison of PSP patients versus PD patients.

a)

PSP vs HC

	+	-	
Global Score PSP <3 (-) SAND	13	24	PPV 86.4%
Global Score PSP ≥3 (+)	38	6	NPV 64.9%
	Sensitivity 74.5%	Specificity 80%	

b)

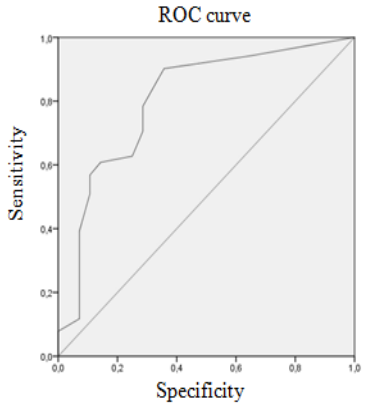


c)

PSP vs PD

	PSP +	- PD	
Global Score PSP <3 (-) SAND	13	20	PPV 82.6%
Global Score PSP ≥3 (+)	38	8	NPV 60.6%
	Sensitivity 74.5%	Specificity 71.4%	

d)



Abbreviations: HC: healthy controls; NPV: negative predictive value; PD: Parkinson's disease; PPV: positive predictive value; PSP: progressive supranuclear palsy; ROC: receiver operating characteristic; SAND: Screening for Aphasia in NeuroDegeneration.

Supplemental table. Spearman's correlation between the PSP-tailored SAND Global Score and non-language tests.

	Spearman's correlation	**P**
Screening of global cognition		
MMSE	-0.058	**<0.001**
MoCA	-0.564	**<0.001**
Memory domain		
RAWLT immediate	-0.296	0.044
RAWLT recall	-0.175	0.238
RCF recall	-0.151	0.345
Attention-executive domain		
CDT	-0.438	0.005
RCF copy	-0.521	**<0.001**
TMT-A	0.645	**<0.001**
Stroop color word test	0.540	**<0.001**

Visuo-spatial domain		
Constructional apraxia	-0.405	0.008
BJLO	-0.645	<**0.001**
Behavioral scales		
BDI-II	0.106	0.511
AES	0.028	0.851
Disease severity		
PSP-rs	0.501	<**0.001**

Significance threshold corrected for multiple comparisons = 0.003; significant differences are highlighted in bold.

Abbreviations: AES: Apathy Evaluation Scale; BDI-II: Beck Depression Inventory II; BJLO: Benton's Judgment of Line Orientation; CDT: Clock Drawing test; MMSE: Mini-Mental State Examinaton; MoCA: Montreal Cognitive Assessment battery; PSP-rs: Progressive Supranuclear Palsy – rating scale; RAVLT: Rey's auditory 15-word learning test; RCF: Rey figure test; TMT-A: Trial Making Test A

Supplemental table. PSP-tailored SAND in PSP, PD and HC

	Continuous scores				Impaired scores (%)			
SAND task	**PSP (51)**	**PD (28)**	**HC (30)**	**p**	**PSP (51)**	**PD (28)**	**HC (30)**	**P**
Naming								
Total	10 (5)	13 (2)	13 (2)	**<0.001** [a,b]	41.2	10.7	6.7	**<0.001** [a,b]
Living	5 (4)	7 (1.8)	7 (1)	**<0.001** [a,b]	31.4	7.1	0	**<0.001** [a,b]
Non-living	6 (2.2)	6.75 (1)	7 (1.5)	**<0.001** [a,b]	54.9	7.1	23.3	**<0.001** [a,b]
Sentence comprehension	7 (3)	8 (0)	8 (1)	**<0.001** [a,b]	49	10.7	10	**<0.001** [a,b]
Single word comprehension								
Total	11 (3.5)	12 (0)	12 (1)	**<0.001** [a,b]	45.1	10.7	6.7	**<0.001** [a,b]
Living	6 (2)	6 (0)	6 (0)	**<0.001** [a,b]	47.1	14.3	6.7	**<0.001** [a,b]
Non-living	6 (1)	6 (1)	6 (1)	**<0.001** [a,b]	25.5	7.1	3.3	0.011
Repetition								
Total	7 (3)	8 (2)	9 (2)	**<0.001** [a,b]	74.2	21.4	6.7	**<0.001** [a,b]
Words	6 (1.5)	6 (0)	6 (0)	**<0.001** [a,b]	25.5	0	7.1	0.003
Non words	2 (3)	2 (2)	3(2)	**<0.001** [a,b]	37.3	14.3	10	0.008
Sentence repetion								
Total	3 (2.5)	4.5 (3)	5 (2)	**<0.001** [a,b]	49	21.4	3.3	**<0.001** [a,c]
Predictable	1 (1)	2 (2)	2 (1)	**<0.001** [a,b,c]	56.9	32.1	13.3	**<0.001** [a,b]
Unpredictable	1 (1)	2 (2)	2 (1)	**<0.001** [a,b]	23.5	7.1	0	0.005
Reading								
Total	14 (6)	15 (2)	16 (1)	**<0.001** [a,b]	47.1	10.7	13.3	**<0.001** [a,b]
Words	11 (4)	12 (1)	12 (0.5)	**<0.001** [a,b]	51	17.9	16.7	0.001
Nonwords	4 (2)	4 (1)	4 (0)	0.003	33.3	10.7	3.3	0.002

Semantic associations	2 (1)	3 (1)	3 (2)	0.002	15.7	0	6.7	0.059
Writing								
Information Units	3 (3)	4 (3)	6 (1)	0.001	26.2	25	0	0.009
Picture description								
Information Units	4 (2.5)	6 (3.75)	5 (3)	0.002	42.2	25	13.3	0.022
PSP-tailored SAND Global Score	8 (8)	1 (4.75)	1 (2)	**<0.001**[a,b]	74.5	28.6	20	**<0.001** [a,b]

Significance threshold corrected for multiple comparisons < 0.001; significant differences are highlighted in bold.
[a]= PSP vs HC p<0.05
[b]= PSP vs PD p<0.05
[c]= HC vs PD p<0.05

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2. Lumping or splitting CorticobasalDegeneration from Progressive Supranuclear Palsy: this is the question

Discussed in *SINDEM* national congress, 2019

2.1 Introduction

Pathological studies suggest corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) are different diseases. And yet, those present several overlapping clinical, genetic and therapeutic aspects. The debate on the clinical differentiation between basal cortical degeneration (CBD) and atypical progressive supranuclear palsy (PSP) is even open, indeed there are opposit points of view on if it can be useful considered PSP and CBD as different disorders. Recently there was a review on symptoms, laboratory tests and differential diagnosis. The autopsy examination shown that, respectively, the 60% and 75% of patients with CBD and PSP were correctly clinically diagnosed and that there were also PSP with similar cortical manifestations to CBD (Amstrong et al., 2014). Specifically, regarding the debate, Alexander et al. (2014) assert that having a corticobasal syndrome does not necessarily mean having a CBD. They saw that there are clinical differences but also mimicry, that the accurate diagnosis is important but also that the Amstrong' criteria is not enough to differentiate CBS patients who have a pathological anatomy from CBD or not. Hoglinger et al. (2018) say that it is not necessary to divide the PSP-CBS and CBS diagnoses, due to largely overlapping spectrum of clinical syndromes, reflecting the variable topography of the cerebral lesions. The initially described and most frequent clinical manifestation of PSP is RS, a combination of progressive postural instability, slowing of saccades, and vertical supranuclear gaze palsy. Although RS it is still believed to be highly specific for PSP, it is acknowledged that patients with CBD can also present a clinical RS manifestation. CBS is a combination of at least one cortical symptom (apraxia, cortical sensory loss, alien limb phenomenon) and at least one extrapyramidal symptom (akinesia, rigidity, dystonia, myoclonus).CBS was initially considered the predominant manifestation of CBD. Mean while, it is known that CBD patients can also present clinical syndromes other than CBS and that CBS patients can have other underlying neuropathologies, including PSP. Progressive parkinsonism (i.e., bradykinesia and rigidity with or without tremor), may also predominate the early

clinical picture in both PSP and CBD. Finally, the non-fluent, “agrammatical” variant of primary progressive aphasia and apraxia of speech have more recently been identified as clinical manifestations of PSP and CBD. Predominant frontal presentations of PSP and CBD may evoke behavioral and cognitive symptoms of frontotemporal dementia. A posterior cortical atrophy syndrome has been reported with diverse. Instead, Ling et al. (2018) affirm that it is necessary to separate them because as both are linked to the protein TAU which however is distributed in different regions. In fact, pathologically, both PSP and CBD have neuronal and glial lesions that are composed primarily of hyper-phosphorylated tau. Nevertheless, the overall patterns of distribution of neuronal and glial lesions differ. In general, cortical and white matter are more affected in CBD, while deep gray matter regions are more affected in PSP. PSP and CBD have their own validated neuropathological diagnostic criteria and are considered as distinct pathological entities. Macroscopically, depigmentation of the substantia nigra is a shared feature. Atrophy of the subthalamic nucleus, superior cerebellar peduncle, and hilum of the cerebellar dentate nucleus are observed in PSP. Many CBD cases have asymmetrical atrophy of parasagittal regions of superior frontal gyrus and superior parietal lobule, affecting pre- and post-central gyri. The cerebral white matter adjacent to the atrophic cortical areas is frequently attenuated with a gray discoloration. Atrophy of the corpus callosum is another common feature. Microscopically, globose neurofibrillary tangles are the typical neuronal tau lesions in PSP, while pretangles are the most common neuronal lesions in CBD and well-formed NFTs are rare. Thread-like processes in white matter are particularly numerous in CBD, distinguishing it from PSP. In PSP, tau accumulates in glial cells as tufted astrocytes and coiled bodies can be numerous in diencephalon and rostral brainstem. In CBD, astrocytic plaques with tau-positive clusters in distal processes are pathognomonic and coiled bodies are less frequent and mainly observed in white matter. Tufted astrocytes and astrocytic plaques are the pathological hallmarks for PSP and CBD, respectively.

Since there are no in vivo biomarkers, we need to re-evaluate the possibility of applying different sets of criteria to classify them as different. The aim of this study was to apply CBS and PSP clinical diagnostic criteria to patients presenting with corticobasal syndrome.

2.2 Methods

Between January, 1st2015 and December, 31st 2018, twelve patients with Corticobasal syndrome were evaluated at our center with an extensive battery of clinical and cognitive assessments.

According to clinical diagnostic criteria 7 were classified as having PSP-CBS variant and 5 as having CBS (1,2).Differences between groups were computed with Mann-Whitney and Fisher's tests. Groups were compared for the following milestones: mild cognitive impairment and dementia, prominent postural instability, vertical supranucleargaze palsy, need to use a walking aid or wheelchair, presence of unintelligible speech and dysphagia.

2.3 Results

The two groups presented similar demographics as well as disease duration and age at onset ($p>0.05$). PSP-CBS showed more severe clinical features compared to CBS according to the PSP rating scale total and subscores ($p<0.05$) (Tab.1). PSP-CBS presented lower scores in cognitive tests evaluating frontal and language cognitive domains ($p<0.05$) (Tab.2). The majority of PSP-CBS patients was either affected by dementia (42%) or presented normal cognition (42%). The majority of CBS patients was either affected by MCI-multiple domain (40%) or presented normal cognition (60%). PSP-CBS had higher frequency of prominent postural instability, vertical supranucleargaze palsy and unintelligible speech ($p<0.05$) **(Fig.1).**

2.4 Conclusion

Our study show that both PSP and CBS criteria can be applied to such patients. Indeed, PSP-CBS and CBS present several overlapping clinical features, with PSP-CBS showing a more severe form of disease in term of motor and cognitive impairment. In absence of in vivo diagnostic biomarkers, there's the need to consider the utility to apply different sets of clinical criteria to classify PSP and CBS as different disorders.

Table 1. Demographic and clinical aspects of PSP-CBS group and CBS group.

	PSP-CBS	**CBS**	**U**	**P**
	Average(DS)	Average(DS)		
Age	69.57±8.59	69.40±8.20	16.00	0.808
Education	9.57±2.87	11.20±6.01	15.00	0.680
Disease duration	5.43±3.64	3.00±0.816	6.50	0.136
PSP-RS History	12.00±4.54	5.4±4.82	5.50	0.051
PSP-RS mental exam	7.42±3.55	2.60±2.96	5.0	**0.040**
PSP-RS blubar	4.42±1.51	0.20±0.44	0.0	**0.004**
PSP-RS ocular motor	12.00±2.94	2.20±2.16	0.0	**0.004**
PSP-RS limb exam	10.71±2.75	7.40±4.21	7.50	0.100
PSP-RS gait	15.14±4.48	7.00±5.00	4.00	**0.025**
PSP-RS total	61.71±15.54	24.80±16.26	0.00	**0.004**
BDI-II	23.25±7.80	24.33±11.06	6.00	1.00
AES	51.00±6.02	37.00±12.70	6.00	0.062
ADL	2.14±2.41	4.40±2.07	8.00	0.118
IADL	1.57±2.07	4.40±2.07	5.50	**0.049**

Significant differences are highlighted in bold.

Abbreviations: CBS: corticobasal syndrome; PSP-rs: Progressive Supranuclear Palsy – rating scale, ADL: Based Activities of Daily Life; AES: Apathy Evaluation Scale; BDI-II: Beck Depression Inventory II, IADL: Instrumental Activities of Daily Life, PSP-CBS: Progressive Supranuclear Palsy with predominant corticobasal syndrome

Table 2.: Cognitive aspects of PSP-CBS group and CBS group.

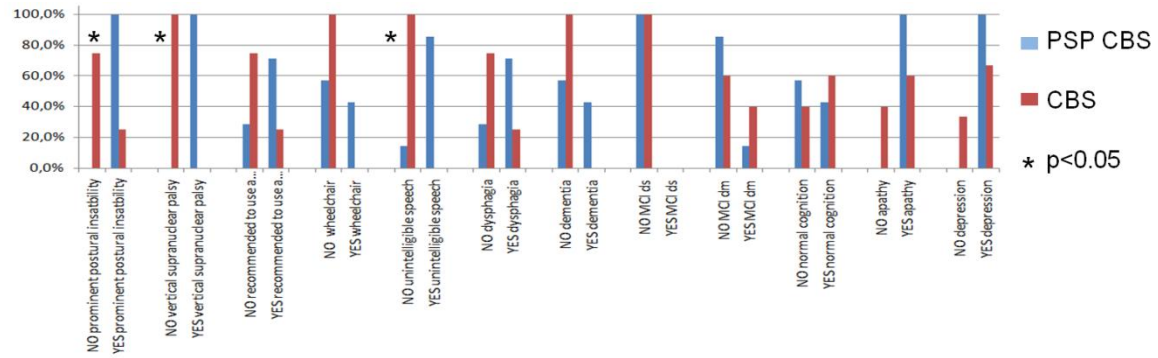
	PSP-CBD	**CBD**	**U**	**P**
	Average(DS)	Average(DS)		
MMSE	22.02±5.34	24.97±5.45	9.50	0.193
MOCA	18.73±4.35	17.45±4.88	12.00	0.917
Semantic fluency	18.42±6.18	31.20±12.63	5.00	**0.041**

TMT-B	500.25±324.11	203.75±63.59	0.00	**0.021**
TMT-BA	256.50±92.17	133.00±49.64	0.00	**0.021**
Word repetition ENPA	7.08±1.22	9.64±0.80	1.00	**0.013**
No-Word repetition ENPA	1.78±1.58	4.14±1.26	3.00	**0.044**

Significant differences are highlighted in bold.

Abbreviations: CBS: corticobasal syndrome, PSP-CBS: Progressive Supranuclear Palsy with predominant corticobasal syndrome; MoCA: Montreal Cognitive Assessment battery; tmt: Trail making test; ENPA: Neuropsychological Examination of Aphasia battery.

Figure 1.: Percentage of Milestones in PSP-CBS group and CBS group.



**Significant differences*

Abbreviations: CBS: corticobasal syndrome;MCI: Mild Cognitive Impairment PSP-CBS: Progressive Supranuclear Palsy with predominant corticobasal syndrome

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3. **Validation of the Italian version of the PSP Quality of Life questionnaire**

Published in *Neurol Sci.* 2019;40(12):2587-2594

3.1 Abstract

Background: Progressive supranuclear palsy (PSP) is a rare rapidly progressive, neurodegenerative disease characterized by falls and ocular movement disturbances. The use of health-related quality of life (HR-QoL) measures allows assessing changes in health status induced by therapeutic interventions or disease progress in neurodegenerative diseases. The PSP-QoL is a 45-item, self-administered questionnaire designed to evaluate HR-QoL in PSP.

Methods and Results: Here, the PSP-QoL was translated into Italian and validated in 190 PSP (96 women and 94 men; mean age ± standard deviation, 72 ± 6.5; mean disease duration, 4.2 ± 2.3) patients diagnosed according to the Movement Disorder Society criteria and recruited in 16 third level movement disorders centers participating in the Neurecanet project. The mean PSP-QoL total score was 77.8 ± 37 (physical subscore, 46.5 ± 18.7; mental subscore, 33.6 ± 19.2). The internal consistency was high (Cronbach's alpha $= 0.954$); corrected item-total correlation was > 0.40 for the majority of items. The significant and moderate correlation of the PSP-QoL with other HR-QoL measures as well as with motor

and disability assessments indicated adequate convergent validity of the scale. Gender and geographic location presented a significant impact on the PSP-QoL in our sample with women and patients from the South of Italy scoring higher than their counterparts.

Conclusion: In conclusion, the Italian version of the PSP-QoL is an easy, reliable and valid tool for assessment of HR-QoL in PSP.

3.2 Introduction

Progressive supranuclear palsy (PSP) is a rare rapidly progressive, neurodegenerative disease characterized by falls and ocular movement disturbances with a prevalence of about 6 per 100,000 and associated with reduced life expectancy, increasing disability, and considerable impact on health-related quality of life (HR-QoL) [1]. Disease severity is commonly assessed with the PSP Rating Scale (PSP-RS) [2].

However, it is now widely acknowledged that patient-reported outcome measurement is an important addition to the evaluation of disease severity both in clinical and research contexts [3, 4]. As such, the use of HR-QoL measures may allow assessment of changes in health status induced by therapeutic interventions or disease progress [3].

The PSP-QoL is a 45-item, self-administered questionnaire designed to evaluate HR-QoL in PSP. The original study validated such instrument in a large sample of PSP native English speakers patient ($N = 188$) demonstrating high construct validity and reliability and potential usefulness as a patient-reported outcome measure in clinical trials [5]. The PSP-QoL includes items covering mobility, dysarthria, dysphagia, visual disturbances, self-care, and activities of daily living representing the physical health status (physical subscore, items 1–22) and questions of emotional, cognitive, and social functioning evaluating the mental health status (mental subscore, items 23–45) [5]. Each item consists of 5 rating categories, ranging from 0 (no problem) to 4 (extreme problem).

The aim of the present study was to validate the Italian version of the PSP-QoL and to investigate the relationships between HR-QoL and demographic and clinical variables in a large sample of PSP patients.

3.3 Methods

Questionnaire translation

The translation of the PSP-QoL in Italian was done according to a stepwise process as follows [6]: (a) the translation from the English original version into Italian was carried out by a movement disorders expert, Italian native speaker, fluent in English (M.P.); (b) the back translation of the Italian version into English was carried out by a native English-speaking translator, fluent in Italian, not involved in the original translation; (c) the English original version was compared with the back-translated one and possible differences were debated, thus resulting in the revision and change of the first Italian version; (d) a comprehension test for the new consensus version was carried out in order to assess if the questionnaire was easy to understand with an independent group of 10 PSP patients from the Centre for Neurodegenerative Diseases (CEMAND), University of Salerno, Italy. All the patients agreed to comment on the comprehensibility and relevance of the questionnaire items; (e) the final Italian version of the PSP-QoL was eventually produced (supplemental material online).

Validation phase

This study was conducted in 16 third level movement disorders centers participating in the Neurecanet project coordinated by the CEMAND, University of Salerno. PSP patients were consecutively enrolled and included if (1) they provided written and signed informed consent; (2) were native Italian-speaking subjects of either sex; (3) were diagnosed with either possible or probable PSP according to the Movement Disorder Society (MDS) criteria [7]; (4) presented a mild to severe form of disease, based on clinical judgment; (5) were accompanied by a native Italian-speaking caregiver. Patients were excluded if they showed evidence of other central nervous system disorders or a degree of depression and/or dementia, which might prevent and/or affect ratings. Each center approached between 61 and 1 patients (total patients approached = 215) and enrolled between 1 and 46 subjects for a total of 190 PSP patients enrolled (Supplemental material online).

A neurologist experienced in movement disorders examined patients at each site and filled in the study questionnaire in order to collect socio-demographic data (age, gender), PSP history, and drug therapy. Disease severity was measured with

the PSP-RS and general cognitive status with the Montreal Cognitive Assessment (MoCA). Disease-related disability was assessed with the Schwab and England Scale (S&E). Participants were asked to complete a booklet consisting of four health measures: PSP-QoL; the EuroQoL questionnaire (EQ-5D) and Visual Analogue Scale (EQ-VAS) of how satisfied the persons felt with their life, two generic HR-QoL measures used in several neurodegenerative disease [8]; the Hospital Anxiety and Depression Scale (HADS) [9].

Before starting the validation phase, involved centers participated in training sessions led by the Coordination Centre (University of Salerno) and aimed at standardizing the assessment methods.

The project was approved by the local Ethics committee.

3.4 Statistical analysis

The following psychometric properties were explored for the PSP-QoL: acceptability, internal consistency, and construct validity. Acceptability was considered appropriate for each PSP-QoL item if there were $\leq 5\%$ of missing values and for the total score and subscores if there were $\leq 15\%$ of the lowest and highest possible scores (floor and ceiling effect). Moreover, skewness of total and two subscores (limits, -1 to $+1$) was determined [6].

Internal consistency was evaluated by means of Cronbach's alpha [10]. A value ≥ 0.70 was considered acceptable [11]. Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation for both PSP-QoL total score and subscores (standard, ≥ 0.40; [12]).

Construct validity was explored with non-parametric Spearman's correlation between PSP-QoL total score and subscores, and other HR-QoL (EQ-5D, EQ-VAS), motor (PSP-RS), cognitive (MoCA), behavioral (HADS), and disability (S&E) assessments.

Spearman's correlation was used to verify the association between PSP-QoL total score and subscores and demographics (age) and PSP clinical history (age at onset and disease duration). The Mann-Whitney or Kruskal-Wallis test with post hoc, as appropriate, was used to verify the impact of gender and geographical location in Italy (North, Center, South) on PSP-QoL total score and subscores.

Correlations were considered strong with coefficient > 0.70 and moderate with a coefficient between 0.30 and 0.70. For the scale's internal validity, it was hypothesized that the correlation between the two subscores of the PSP-QoL would stand at 0.30–0.70. The significance threshold was set at $p \leq 0.05$.
The statistical analysis was performed with SPSS (Version 23).

3.5 Results

Two hundred and fifteen patients were included in the study, but 25 were excluded because of severe cognitive and/or motor impairment possibly preventing and/or affecting ratings. The Italian version of the PSP-QoL was administered to 190 PSP patients (96 women and 94 men, of whom 160 (84.2%) on dopaminergic treatment). The mean ± standard deviation PSP-QoL total score was 77.8 ± 37 and the median ± interquartile range (IQR) was 77.5 ± 45. The mean PSP-QoL physical subscore was 46.5 ± 18.7 and the median was 46 ± 25.5. The mean PSP-QoL mental subscore was 33.6 ± 19.2 and the median was 31.5 ± 26. Details on the enrolled cohort are displayed in Table 1.

Acceptability

Ninety-eight percent of data were totally computable and 2% were missing values. The percentage of missing values was ≤ 5% for all items. In the whole PSP sample, neither the ceiling nor the floor effects were observed for the PSP-QoL total score (lowest possible score = 0, 4%; highest possible score = 197, 0.5%) nor for the PSP-QoL physical subscore (lowest possible score = 7, 0.5%; highest possible score = 97, 0.5%) or the PSP-QoL mental subscore (lowest possible score = 0, 1.5%; highest possible score = 100, 1%). The skewness of total and two subscores of PSP-QoL was within the standard limits (PSP-QoL total score = 0.4, PSP-QoL physical subscore = 0.1, PSP-QoL mental subscore = 0.7).

Reliability

Cronbach's alpha was 0.954 and, thus, it was considered acceptable for internal consistency. No item improved Cronbach's alpha if removed. Item-PSP-QoL total score correlation was ≥ 0.40 for all questions except for questions 5 (0.373), 7 (0.320), 10 (0.269), 29 (0.350), and 39 (0.338) (Table 2). Item-PSP-QoL physical

subscore correlation was ≥ 0.40 for all questions except for questions 5 (0.376), 7 (0.323), and 10 (0.335) (Table 2). Item-PSP-QoL mental subscore correlation was ≥ 0.40 for all questions (Table 2).

Convergent construct validity

As for the PSP-QoL total score, the non-parametric Spearman's correlation showed no relation with demographic, education, or PSP clinical history. A moderate correlation emerged with PSP-RS, MoCA, S&E, and other health-related quality of life measures, but with the EQ-5D pain subscale. No correlation with HADS subscores was found (Table 3).

As for the PSP-QoL physical subscore, no correlation was found with demographic or PSP clinical history. A moderate correlation emerged with other health-related quality of life measures, but with the EQ-5D pain subscale. A strong correlation of PSP-QoL physical subscore with PSP-RS and S&E was found. No correlation with HADS subscores was shown (Table 3).

As for the PSP-QoL mental subscore, no correlation was shown with demographic or PSP clinical history. A moderate correlation emerged with PSP-RS, MoCA, S&E, and other health-related quality of life measures, but with the EQ-5D pain subscale. No correlation with HADS subscores was found (Table 3).

The correlation between PSP-QoL physical and mental subscores was moderate (rho = 0.592).

The Mann-Whitney test showed a significant impact of gender on the PSP-QoL total score with women scoring higher than man (Table 4). PSP-RS did not present gender differences (Table 4). The Kruskal-Wallis test showed a significant impact of geographic location on PSP-QoL total score and both subscores with patients from the South of Italy scoring higher than those from both the Center and North (Table 4). PSP-RS presented similar differences according to geographical location (Table 4).

3.6 Discussion

The present study showed that the Italian version of the PSP-QoL is acceptable, reliable, and easily applicable in the Italian PSP population. The scale as a whole

showed high acceptability since data were computable for 98% and the percentage of missing values was ≤ 5% for all items. The acceptability of the Italian version is also supported by the absence of both ceiling and floor effects for the PSP-QoL total score and the physical and mental subscores, as reported in the original study [5].

The internal consistency of the Italian version of the PSP-QoL is high, acceptable (alpha = 0.954; item-PSP-QoL total score correlation ≥ 0.40 for all items except for 5 (falls), 7 (opening eyes), 10 (drooling), 29 (sleeping issues not related to movements), and 39 (memory problems)), and close to values obtained in the original study [5]. The lack of significant item-total correlation for few items may suggest either that such questions were not able to measure the related problems or the corresponding issues were less pronounced compared with other problems included in the questionnaire. The latter hypothesis is supported by the high percentage of the lowest possible scores for items 5 (15.6%), 7 (51.8%), 10 (47.7%), 29 (27.1%), and 39 (33.3%). However, item 39 presented an adequate interrelation with the PSP-QoL mental subscore, thus suggesting this item is more related to the corresponding subscore than the total score (Table 2).

As for convergent and divergent construct validity, the PSP-QoL total score and both subscores showed unnoticeable association with demographics, education, and PSP clinical history. Such low correlation may be indicative of a satisfactory divergent validity and suggest that the scale is suitable for PSP patients of any age, age at onset and disease duration.

The adequate construct validity of the Italian version of the PSP-QoL was supported by a moderate correlation between the total score and both subscores of the PSP-QoL with other HR-QoL measures (i.e., EuroQoL 5D and EQ-VAS). Furthermore, the PSP-QoL total score and mental subscore presented a moderate association with severity of disease as assessed with the PSP-RS and S&E, while in the case of the physical subscore, the association was strong. Indeed, these data support the hypothesis that both subscores are related but measure different aspects of disease. On the other hand, the PSP-QoL total score and subscores present also a moderate association with a cognitive measure as the MoCA, while no association was shown with HADS for any PSP-QoL score suggesting the scale does not reflect anxiety and depression burden in PSP patients.

Internal construct validity was supported by the moderate interscale correlation between the physical and mental subscales (0.637), as in the original study, implying that the two PSP-QoL subscales measure related but different health constructs [5].

Differently from the original study, gender has a significant impact on PSP-QoL total score in our sample. Different explanations may account for such discrepancy. First, similarly to other neurodegenerative diseases, it is likely gender differences in PSP exist, although there is scant of such studies in PSP [13]. Second, the majority of the cohort of the original study was based in the UK [5]. The cultural background has a well-known impact on gender discrepancies. Finally, although we did not find differences by gender for the PSP-RS (Table 4), we cannot exclude women in our cohort presented a more severe form of the disease not captured by the PSP-RS.

We also showed significant differences for the PSP-QoL total score and subscores in relation to the geographic location with patients from the South of Italy scoring higher than those from both the Center and North (Table 4). First, we cannot exclude some cultural background differences may in part account for such result. Also, such data can be explained in light of both the demographic and disease-related differences shown by patients according to geographic location. As such, patients from the North of Italy were older, with older age at onset, higher MoCA and HADS scores, and lower PSP-RS. On the other hand, disease duration, gender distribution as well as disease-related disability, and quality of life as assessed with the EQ-VAS did not show significant differences over the country (Table 1). Although interesting, regional differences in such measures were out of the scope of the present work, which aimed at validating the PSP-QoL for Italian-speaking PSP patients. Thus, these data need to be further explored.

Our study has several strengths. Firstly, this is the largest sample of Italian PSP patients collected to date, as large as in the original study [5]. Secondly, several centers across Italy joined the study; thus, the results are representative of all the country. On a total of 215 patients approached, Movement Disorders Centers located in the North, Center, and South equally contributed to the study according to local possibilities (Supplemental material) demonstrating the feasibility of an Italian network on a rare, neurodegenerative disease [14]. Furthermore, all included

patients underwent a thorough evaluation by a movement disorder expert in a third level center and were diagnosed according to recent MDS criteria [7, 15]. Finally, the low proportion of missing data increases the reliability of our findings.

Our study has limitations. Although we sought to include patients at all stages of PSP, it is likely that patients in more advanced stages who cannot respond accurately on their own, particularly those with cognitive impairment or unable to communicate, were underrepresented in our sample.

In conclusion, the PSP-QoL Italian version is an applicable and valid tool to measure HR-QoL in Italian PSP patients.

Table 1 Demographics and clinical features of the enrolled cohort

	The whole sample (190)	**North (68)**	**Center (41)**	**South (81)**	***P***
Age	73 (8.5)	75 (9.83)	72 (6)	72 (8)	0.014*
Gender (M/W, %)	94/96 (49.5/50.5)	29/39	22/19	43/38	0.400
Education	8 (8)	5 (6)	5 (3)	8 (8)	0.137
Age at onset	69 (8)	70 (9)	68 (6)	67 (10)	0.008^
Disease duration	4 (3)	4 (3)	4 (3)	4 (3)	0.223
PSP-RS	38 (21)	35 (18)	41.5 (16)	44 (25)	0.011@
MoCA	18 (8)	18 (8)	17 (5)	16.5 (11)	0.004§
S&E	50 (40)	50 (40)	40 (30)	45 (38)	0.413
EQ-VAS	50 (30)	50 (26)	50 (30)	40 (50)	0.966
HADS anxiety score	7 (6)	7 (6)	8 (5)	3 (7)	< 0.001°
HADS depression score	11 (6)	11 (6)	11 (3)	6 (13)	< 0.001ç

1. Data are expressed in median (interquartile range), unless otherwise specified
2. *EQ-VAS* Visual Analogue Scale, *HADS* the Hospital Anxiety and Depression Scale, *IQR* interquartile range, *M* men, *MoCA* the Montreal Cognitive Assessment, *PSP-RS* Progressive Supranuclear Palsy Rating Scale, *S&E* the Schwab and England Scale, *W* women
3. *North versus Center, $p = 0.015$; North versus South, $p = 0.011$; Center versus South, $p = 0.996$
4. ^North versus Center, $p = 0.034$; North versus South, $p = 0.003$
5. @North versus Center, $p = 0.042$; North versus South, $p = 0.006$
6. §North versus South, $p = 0.001$
7. °North versus South, $p < 0.001$; Center versus South, $p < 0.001$
8. ςNorth versus South, $p < 0.001$; Center versus South, $p < 0.001$

Table 2 Item-total correlation for the PSP-QoL total score and physical and mental subscores

Item	PSP-QoL total score	PSP-QoL physical subscore	PSP-QoL mental sub score
1	0.677*	0.748*	–
2	0.600*	0.649*	–
3	0.642*	0.758*	–
4	0.525*	0.563*	–
5	0.373*	0.376*	–
6	0.459*	0.513*	–
7	0.320*	0.323*	–
8	0.652*	0.696*	–
9	0.594*	0.641*	–
10	0.269*	0.335*	–
11	0.632*	0.615*	–
12	0.592*	0.629*	–
13	0.723*	0.775*	–
14	0.703*	0.792*	–
15	0.489*	0.541*	–
16	0.634*	0.637*	–
17	0.524*	0.650*	–
18	0.636*	0.730*	–
19	0.601*	0.669*	–
20	0.498*	0.602*	–
21	0.565*	0.642*	–
22	0.382*	0.490*	–
23	0.705*	–	0.685*
24	0.658*	–	0.705*
25	0.585*	–	0.678*

26	0.624*	–	0.723*
27	0.465*	–	0.537*
28	0.516*	–	0.615*
29	0.350*	–	0.420*
30	0.439*	–	0.526*
31	0.610*	–	0.667*
32	0.616*	–	0.709*
33	0.502*	–	0.591*
34	0.541*	–	0.576*
35	0.550*	–	0.632*
36	0.464*	–	0.548*
37	0.550*	–	0.695*
38	0.508*	–	0.517*
39	0.338*	–	0.451*
40	0.439*	–	0.529*
41	0.647*	–	0.629*
42	0.578*	–	0.644*
43	0.607*	–	0.706*
44	0.648*	–	0.754*
45	0.698*	–	0.737*

1. *$p < 0.001$
2. *PSP-QoL* Progressive Supranuclear Palsy Quality of Life Questionnaire

Table 3 Convergent validity of the PSP-QoL total score and subscores

	PSP-QoL total score	***p***	**PSP-QoL physical subscore**	***p***	**PSP-QoL mental subscore**	***P***
Age	0.025	NS	0.004	NS	− 0.036	NS
Education	− 0.094	NS	− 0.080	NS	− 0.079	NS
Age at onset	− 0.060	NS	− 0.103	NS	− 0.092	NS
Disease duration	0.223	< 0.05	0.307	< 0.001	0.143	NS
EuroQoL 5D motility	0.445	< 0.001	0.491	< 0.001	0.343	< 0.001
EuroQoL 5D self-care	0.668	< 0.001	0.700	< 0.001	0.547	< 0.001
EuroQoL 5D usual activities	0.500	< 0.001	0.527	< 0.001	0.424	< 0.001
EuroQoL 5D	0.275	< 0.001	0.236	< 0.05	0.242	< 0.05

pain						
EuroQoL 5D anxiety	0.471	< 0.001	0.324	< 0.001	0.519	< 0.001
EuroQoL 5D total score	0.486	< 0.001	0.447	< 0.001	0.483	< 0.001
EuroQoL EQ-VAS	−0.534	< 0.001	− 0.449	< 0.001	− 0.552	< 0.001
PSP-RS	0.656	< 0.001	0.719	< 0.001	0.451	< 0.001
MoCA	−0.404	< 0.001	− 0.394	< 0.001	− 0.311	< 0.001
HADS anxiety score	0.239	< 0.001	0.194	< 0.05	0.299	< 0.001
HADS depression score	0.246	< 0.001	0.235	< 0.05	0.280	< 0.001
S&E	−0.625	< 0.001	− 0.720	< 0.001	− 0.462	< 0.001

EQ-VAS the EuroQoL Visual Analogue Scale, *HADS* the Hospital Anxiety and Depression Scale, *MoCA* the Montreal Cognitive Assessment, *NS* not significant, *PSP-RS* Progressive Supranuclear Palsy Rating Scale, *S&E* the Schwab and England Scale

Table 4 Impact of gender and geographic location in Italy on PSP-QoL total score and physical and mental subscores

Variable	Type	PSP-QoL total score	PSP-QoL physical subscore	PSP-QoL mental subscore	PSP-RS
Gender	Men ($N = 94$)	70 (42)	44 (26.5)	28 (20.5)	39 (21)
	Women ($N = 96$)	87 (49)	50 (25)	33 (33.5)	42 (23)
	p	0.035	0.053	0.086	0.169
Geographic location	North ($N = 68$)	73 (41)	44 (23)	30 (28)	See Table 1
	Center ($N = 41$)	69 (38)	42.5 (27.2)	26 (20)	

	South ($N = 81$)	93 (46)	54 (28)	37 (32)	
	p	0.003*	0.012[§]	0.021[°]	

1. Data are expressed in median (interquartile range)
2. *Center versus South, $p = 0.005$; North versus South, $p = 0.03$;
3. [§]Center versus South, $p = 0.002$; North versus South, $p = 0.03$
4. [°]Center versus South, $p = 0.271$

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4. Validation of the Italian version of carers' quality-of-life questionnaire for parkinsonism (PQoL Carer) in progressive supranuclear palsy

Published in *Neurol Sci.* 2019;40(10):2163-2169.

4.1 Abstract

Progressive supranuclear palsy (PSP) is a rare, rapidly progressive, neurodegenerative disease characterized by falls and ocular movement disturbances. Caring for a partner or relative who suffers from PSP entails a strenuous and demanding task, usually lasting for years that affects carers' everyday life routines and emotional and social well-being. The 26-item Parkinsonism Carers QoL (PQoL Carer) is a self-administered, concise instrument evaluating the quality of life of caregivers of patients with atypical parkinsonism (both PSP and multiple system atrophy). Here, the PQoL Carer was translated into Italian and validated in 162 carers of PSP patients (54.3% women; mean age (standard deviation), 62.4 (15.4)) diagnosed according to the Movement Disorder Society criteria and recruited in 16 third-level movement disorders centers participating in the Neurecanet project. The mean PQoL total score was 40.66 ± 19.46. The internal consistency was excellent (Cronbach's alpha $= 0.941$); corrected item-total correlation was > 0.40 for all the items. A correlation with other health-related quality of life measures as well as with behavioral assessments was shown suggesting adequate convergent validity of the scale. PQoL also correlated with patients' severity of disease. The discriminant validity of the scale

was evidenced by its capacity to differentiate between carers with varying levels of self-reported health ($p < 0.001$). In conclusion, the Italian version of the PQoL Carer is an easy, consistent, and valid tool for the assessment of the quality of life in carers of PSP patients.

4.2 Introduction

Progressive supranuclear palsy (PSP) is a rare, rapidly progressive, neurodegenerative disease characterized by falls and supranuclear vertical palsy with a prevalence of about 6 per 100,000 and associated with reduced life expectancy, increasing disability, and considerable impact on health-related quality of life (HR-QoL) [1]. Caregivers (usually relatives and partners) are profoundly involved in the care of those patients with a disruptive impact on different aspects of their quality of life [2]. Although carers play a pivotal role in PSP patients' natural history, there is a scant of studies assessing the distinct features of caregiving in this area [3].

The 26-item Parkinsonism Carers QoL (PQoL Carer) is a self-administered, concise instrument evaluating HR-QoL of caregivers of patients with atypical parkinsonism (both PSP and multiple system atrophy). Each item consists of 5 rating categories, ranging from 0 (no problem) to 4 (extreme problem) [4]. The original study validated such instrument in a large sample of native English speaker carers of PSP patients ($N = 187$) demonstrating high acceptability, construct validity, and potential usefulness as a carer-reported outcome measure in clinical trials [4]. A PQoL Carer cut off > 62 has been proposed for identifying carers with a greater burden as well as severe anxiety and/or depression [5].

The aim of the present study was to validate the Italian version of the PQoL Carer in a large sample of caregivers of PSP patients.

4.3 Methods

Questionnaire translation

The translation of the PQoL Carer in Italian was done according to a stepwise process as follows [6]: (a) the translation from the English original version into Italian was carried out by a movement disorders expert and Italian native speaker, fluent in English (M.P.); (b) the back translation of the Italian version into English

was carried out by a native English-speaking translator, fluent in Italian, not involved in the original translation; (c) the English original version was compared with the back-translated one and the possible differences were debated, thus resulting in the revision and changing of the first Italian version; (d) a comprehension test for the new consensus version was carried out in order to assess if the questionnaire was easy to understand with an independent group of 10 carers of PSP patients from the Center for Neurodegenerative Diseases (CEMAND), University of Salerno, Italy. All the carers agreed to comment on the comprehensibility and relevance of the questionnaire items; and (e) the final Italian version of the PQoL Carer was produced (Table 1).

Validation phase

This study was conducted in 16 third-level movement disorders centers participating in the Neurecanet project coordinated by the CEMAND, University of Salerno. Carers of PSP patients were consecutively enrolled and included if (1) they provided written and signed informed consent; (2) were native Italian-speaking subjects of either sex; and (3) were caregivers of PSP patients diagnosed with either possible or probable PSP according to the Movement Disorder Society (MDS) criteria [7]. Each center enrolled between 1 and 25 subjects for a total of 162 carers of PSP patients.

Enrolled subjects completed the PQoL Carer together with a few questions including age, gender, their relationship with the patient, hours spent daily with the patient, and whether they were living in the same premises with the patient. Carers were also asked to compare their current state of health to that 12 months ago, by indicating whether it was (1) better, (2) much the same, or (3) worse. They also completed the EQ-5D (three-level version) [8], a 5-item standardized self-report health status instrument assessing the individual's level of health status on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); the EQ-VAS (visual analogue scale), a self-rating of overall health ranging from 0 (worst imaginable health state) to 100 (best imaginable health state); and the Hospital Anxiety and Depression Scale (HADS) [9], an instrument comprising 14 items, seven of which measure anxiety (HADS-A) and the remaining seven depression (HADS-D). The scores on each scale range from 0

to 21, with higher scores on each scale indicating more anxiety or depression, respectively. Corresponding PSP patients were evaluatedwith the PSP rating scale (PSP-RS) by a movement disorders specialist [10].

Before starting the validation phase, involved centers participated in a training session led by the Coordination Center (University of Salerno) and aimed at standardizing the assessment methods.

The project was approved by the local Ethics committee.

4.4 Statistical analysis

The following psychometric properties were explored for the PQoL Carer: acceptability, internal consistency, and construct validity. Acceptability was considered appropriate for each PQoL Carer item if there were $\leq 5\%$ of missing values and $\leq 15\%$ of the respondents with the lowest and highest possible scores (floor and ceiling effect). Moreover, skewness of total score (limits, -1 to $+1$) was determined [6].

Internal consistency was evaluated by means of Cronbach's alpha [11]. A value ≥ 0.70 was considered acceptable [12]. Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation (standard, ≥ 0.40; [13]).

The convergent validity of the scale was evaluated by correlation (Spearman's correlation test) of PQoL Carer with (a) patients' PSP-RS, based on the assumption that the degree of severity of the patient's motor condition impacts on the carer's HR-QoL [4] and (b) EQ-5D and the EQ-VAS, as well as the HADS.

The discriminant validity of the scale was evaluated with the ANOVA test: we evaluated whether PQoL Carer significantly differentiated between (a) carers with varying levels of current health problems compared with that of 12 months ago (better, much the same, worse) and (b) carers with varying health levels based on their scores on the EQ-VAS (EQ-VAS score less than 35, less than 50, less than 70, 70 or greater).

The *T* test or ANOVA test with post hoc, as appropriate, was used to verify the impact of gender and geographical location in Italy (North, Center, South) on PQoL Carer.

Based on the PQoL Carer cut-off value of 62 [5], caregivers were divided into two groups: subjects with reduced QoL and subjects with preserved QoL. The two groups were compared on demographic and behavioral variables.

Correlations were considered strong with coefficient > 0.70, moderate with coefficient between 0.30 and 0.70, and negligible with coefficient < 0.30. Significance level was set at $p \leq 0.05$.

Statistical analysis was performed with SPSS (Version 23).

4.5 Results

One hundred sixty-two carers of PSP patients (54.3% women) were included in the present study. Mean (standard deviation) age was 62.4 (15.4) years old, 92% were patients' relatives spending together with the patient a mean of 16.5 (9.1) h. Seventy-two percent declared to live on the same premises as the patients. The mean ± standard deviation PQoL Carer was 40.66 ± 19.46 and the median ± interquartile range (IQR) was 39.50 ± 28.

Acceptability

A total of 99.86% of data were totally computable and 0.14% were missing values. The percentage of missing values was $\leq 5\%$ for all items. Neither ceiling nor floor effects were observed for the PQoL Carer (lowest possible score = 1, 0.6%; highest possible score = 97, 0.6%). The skewness of PQoL Carer was within the standard limits (score = 0.271).

Reliability

Cronbach's alpha was 0.941 indicating a high level of internal consistency. No item improved the value of Cronbach's alpha if removed. Item-PQoL Carer correlation was ≥ 0.40 for all items; items 18 ($r = 0.762$) and 19 ($r = 0.757$) had the highest correlation coefficient (Table 1).

Convergent construct validity

A moderate correlation of the PQoL Carer score was pointed out with patients' severity of disease (PSP-RS), with other HR-QoL measures such as EQ-VAS and three dimensions of the EQ-5D (mobility, usual activities, and anxiety/depression), whereas a significant but poor correlation was found with self-care and pain/discomfort dimensions of the EQ-5D. Moreover, PQoL Carer score moderately correlated with the score on HADS-A and HADS-D. No significant correlation was found between PQoL Carer score and carer's age (Table 2).

The analysis showed no significant impact of either gender or geographic location on PQoL Carer (Table 3). The ANOVA test showed a significant impact on the variable "Carers' health today compared with health 12 months ago" on PQoL Carer; in particular, carers reporting worse condition showed higher values than those reporting much the same condition (Table 3). The Kruskal-Wallis test showed a significant impact on the variable "Carers' rating of overall health: EQ-VAS score" on PQoL Carer; in particular, carers having an EQ-VAS score of 70 or greater showed lower values than those having an EQ-VAS score less than 35, less than 50, and less than 70 (Table 3).

Twenty-six (16%) of carers scored > 62 on the PQoL Carer. Those carers presented worse condition compared with that 12 months before, higher HADS-A and HADS-D as well as lower EQ-VAS compared with carers scoring ≤ 62 on the PQoL Carer (Table 4). Furthermore, corresponding patients presented higher PSP-RS (Table 4).

4.6 Discussion

Here, we showed that the Italian version of the PQoL Carer is acceptable and easily applicable in the Italian carers of PSP patients. This is also the first application of the PQoL Carers in an independent sample after the original study supporting high levels of reliability of the scale [4].

The scale as a whole showed high acceptability since data were computable for 99.86% and the percentage of missing values was ≤ 5% for all items. The acceptability of the Italian version is also supported by the absence of both ceiling

and floor effects for the PQoL Carer total score, as reported in the original study [4].

The internal consistency of the Italian version of the PQoL Carer is high and acceptable (alpha = 0.941) with an item-total score correlation of ≥ 0.40 for all items with values close to those obtained in the original study [4].

As for convergent and divergent construct validity, the PQoL Carer showed unnoticeable association with demographics. Such low correlation may be indicative of a satisfactory divergent validity and suggests the scale is suitable for carers of PSP patients of any age.

Evidence of adequate construct validity has been shown for the Italian version of the PQoL Carer. The construct validity was supported by a moderate correlation between PQoL Carer total score and other HR-QoL measures such as the EQ-5D and EQ-VAS.

Similar to the original study [4], the PQoL Carer also presented a moderate association with severity of the disease of PSP patients, as assessed with the PSP-RS. Indeed, these data support the hypothesis that HR-QoL of carers is related to patients' severity of disease.

Furthermore, we showed a moderate association between PQoL Carer and HADS both anxiety and depression scores, confirming a relationship between carers' HR-QoL and such behavioral symptoms [4, 5].

Neither gender nor geographic location in Italy had a significant impact on PQoL Carer in our sample, further supporting the reliability of the questionnaire for both sexes and all over the country.

The ANOVA test provided supportive evidence of the discriminant validity of the PQoL Carer. Scores on the scale significantly differentiate between carers with varying levels of the variable "current state of health compared with health 12 months ago" ($p < 0.001$) and carers with varying levels of self-reported health based on their scores on the EQ-VAS ($p < 0.001$) (Table 3).

Our study has several strengths. First, this is the largest sample of Italian carers of PSP patients collected to date, as large as in the original study [4]. Second, several centers across Italy joined the study; thus, the results are representative of all the country. Furthermore, all included carers had the corresponding patients evaluated in a third-level movement disorders center according to the MDS criteria as well as

PSP-RS [7, 14]. Finally, the low proportion of missing data increases the validity of our findings.

Our study has limitations. Although we sought to include caregivers of patients at all stages of PSP, it is likely that carers of patients in more advanced stages who cannot attend outpatient clinics were underrepresented in our sample.

In conclusion, the PQoL Carer Italian version showed high acceptability and good validity and reliability in assessing HR-QoL in carers of PSP patients. Further use of such assessment both in clinical and in research context is supported by its ease of application as well as its adequate psychometric properties.

Table 1 Item-total correlation of the PQoL Carer

Item	**Item-total correlation**
1. Per prendersi cura del Suo parente/partner necessita di uno sforzo fisico?	**0.538***
2. E' difficile prendersi cura dei Suoi problemi di salute?	**0.714***
3. Ha avuto problemi di salute (es. ha sofferto di mal di schiena o dolori articolari)?	**0.468***
4. Pensa che prendersi cura di una persona malata sia stressante?	**0.714***
5. Si sente affaticato o stanco?	**0.710***
6. Si sente frustrato o annoiato?	**0.716***
7. Si sente triste?	**0.663***
8. Si sente solo o abbandonato?	**0.629***
9. Si sente arrabbiato o tradito?	**0.651***
10. Sente che il Suo sonno è disturbato?	**0.621***
11. Si preoccupa del Suo parente/partner?	0.618*

Item	Item-total correlation
12. Pensa che sia emotivamente difficile avere a che fare con i problemi fisici del suo parente/partner?	0.521*
13. La comunicazione con il Suo parente/partner è peggiorata?	0.586*
14. Il suo rapporto con il suo parente/partner è cambiato?	0.563*
15. Pensa sia difficile avere a che fare con il cambio di personalità del suo parente/partner?	0.479*
16. Pensa sia difficile tollerare il cambio di ruoli tra Lei e il Suo parente/partner?	0.684*
17. Pensa che la Sua intimità sia stata compromessa?	0.518*
18. Si sente in trappola?	0.762*
19. Sente di non fare molte cose per se stesso/a ultimamente?	0.757*
20. E' diventato difficile fare le cose spontaneamente?	0.638*
21. Esce di meno?	0.705*
22. Trova che la vita sia noiosa?	0.567*
23. Vede meno amici e familiari?	0.661*
24. La Sua vita familiare ha risentito della situazione?	0.687*
25. Sente di prendersi più responsabilità di quelle che dovrebbe?	0.566*
26. Pensa di non avere abbastanza supporto?	0.639*

*Correlation is significant at level 0.01 (two-tailed)

Table 2 Convergent validity of the PQoL Carer

	Spearman's correlation	*p*

	Spearman's correlation	*p*
Age	0.052	0.526
Patients' PSP-RS	0.308	< 0.001
EQ-5D mobility	0.312	< 0.001
EQ-5D self-care	0.191	0.026
EQ-5D usual activities	0.352	< 0.001
EQ-5D pain/discomfort	0.292	< 0.001
EQ-5D anxiety/depression	0.410	< 0.001
EQ-VAS	− 0.503	< 0.001
HADS-A	0.401	< 0.001
HADS-D	0.414	< 0.001

Table 3 Impact of gender and geographic location on PSPQoL Carer and the distribution of scores of the PQoL Carer across levels of carers' current health compared with health 12 months ago and self-ratings of overall health

Variable	**Type**	**PQoL Carer**
Gender	Men (*N* = 74)	39 (16.4)
	Women (*N* = 88)	42 (21.6)
	P	0.333
Geographic location	North (*N* = 57)	43.1 (17.4)
	Center (*N* = 52)	39.4 (20.4)
	South (*N* = 53)	39.2 (20.5)
	P	0.487
Carers' health today compared with health 12 months ago	Better (*N* = 6)	40.6 (13.5)
	Much the same (*N* = 71)	30.4 (17.4)
	Worse (*N* = 82)	49.7 (17.2)
	P	< 0.001*
Carers' rating of overall health: EQ-	Less than 35 (*N* = 8)	62.2 (10.9)

Variable	Type	PQoL Carer
VAS score	Less than 50 ($N = 28$)	51.6 (20.5)
	Less than 70 ($N = 13$)	49.1 (15.5)
	70 or greater ($N = 95$)	33.4 (15.6)
	P	< 0.001°

Values are shown in mean (standard deviation), unless otherwise specified

*Much the same versus worse, $p < 0.001$; better versus much the same, $p = 0.117$; better versus worse, $p = 0.253$

°Less than 35 versus less than 50, $p = 0.118$; less than 35 versus less than 70, $p = 0.110$; less than 35 versus 70 or greater, $p < 0.001$; less than 50 versus less than 70, $p = 0.801$; less than 50 versus 70 or greater, $p < 0.001$; less than 70 versus 70 or greater, $p = 0.002$

Table 4 Comparison between the two groups of carers based on the PQoL cut-off of 62

	PQoL ≤ 62	PQoL > 62	*P*
Age	62.5 (15.1)	62 (17.2)	0.891
Women/men, *n* (%)	69/67 (50.7/49.3)	19/7 (73.1/26.9)	0.052
Living in the same premises as the patients, yes/no, *n* (%)	96/38 (71.6/28.4)	22/4 (84.6/15.4)	0.225
Hours spent daily with the patient	16.1 (9.2)	18.8 (8.2)	0.160
Patients' PSP-RS	39.9 (15)	49 (20.9)	0.028
HADS-A	6 (4)	9.3 (4.6)	< 0.001
HADS-D	6.1 (3.5)	9.4 (4.6)	< 0.001
EQ-VAS	72.2 (16.5)	48.9 (21.4)	< 0.001
Carers' health today compared with health 12 months ago (better/much the same/worse)	6/67/60 (4.5/50.4/45.1)	0/4/22 (0/15.4/84.6)	< 0.001

Values are shown in mean (standard deviation), unless otherwise specified

EQ-VAS, Euroqol visual analogue scale; *HADS-A*, Hospital Anxiety Depression Scale – anxiety; *HADS-D*, Hospital Anxiety Depression scale – depression; *PQoL*, quality-of-life questionnaire for parkinsonism; *PSP-RS*, progressive supranuclear palsy rating scale.

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Chapter IV

MULTIPLE SYSTEM ATROPHY

1.Evolution of neuropsychological profile in motor subtypes of multiple system atrophy

Published in *Parkinsonism Relat Disord*. 2019;70:67-73.

1.1 Abstract

Introduction: Cognitive deficits and neuropsychiatric symptoms occur in parkinsonian and cerebellar subtypes of Multiple System Atrophy (MSA-P and MSA-C). These symptoms have been investigated mainly in cross-sectional studies. The present 1-year follow-up study aimed at evaluating the evolution of cognitive and neuropsychiatric profile in patients with MSA-C and MSA-P.

Methods: Twenty-nine patients with MSA-P, 21 with MSA-C and 30 healthy subjects (HCs) underwent a neuropsychological battery and questionnaires assessing depression and apathy (T0). After 1 year (T1), patients with MSA-C and MSA-P underwent the same neuropsychological and neuropsychiatric tools employed at T0.

Results: At T0, MSA-P and MSA-C groups were more depressed and apathetic and performed worse on tests assessing repetition abilities, executive and attentive functions than HCs. MSA-P and MSA-C groups did not differ on cognitive variables and neuropsychiatric scales. At T1, a significant worsening in spatial planning and psychomotor speed in MSA-C group and a significant worsening in memory, spatial planning, repetition abilities and functional autonomy in MSA-P

group were found. The prevalence of apathy increased in both subtypes, whereas the prevalence of depression was reduced in MSA-C and relatively consistent in MSA-P.

Conclusions: The finding revealed a wide-ranging worsening of cognitive functions in MSA-P and a significant decline in processing speed in MSA-C. These results underline the relevance of evaluating cognitive and psychiatric features of MSA over the course of the disease in the daily clinical practice.

1.2 Introduction

Multiple System Atrophy (MSA) is a rare progressive neurodegenerative disease characterized by a combination of autonomic dysfunctions, parkinsonism, and ataxia [1]. MSA is classified in two different motor subtypes: the parkinsonian subtype if parkinsonism is the predominant feature (MSA-P) and the cerebellar subtype if cerebellar features predominate (MSA-C) [2]. MSA includes both motor and non-motor symptoms such as cognitive deficits, which begin to be considered an integral part of the disease [3]. Cognitive deficits related to MSA include mainly executive dysfunctions [4,5], and are a consequence of an impairment of prefronto-subcortical circuits [6,7]. Even memory, attention and visuospatial functions are slightly impaired in MSA patients with respect to executive dysfunctions [4,5,8]. Since cognitive deficits in neurodegenerative diseases such as Parkinson's Disease (PD) may precede a cognitive decline or be a stable condition [9], the occurrence and evolution of cognitive deficits in MSA deserve to be investigated, even in the two motor subtypes of MSA.

Until now, cognitive profile associated with MSA has mainly been investigated by cross-sectional studies, whereas it has been evaluated in a very few longitudinal studies characterized by some limitations [[10], [11], [12]]. In a longitudinal study, Soliveri et al. [10] evaluated the progression of cognitive impairment in several parkinsonian syndromes (PD, progressive supranuclear palsy (PSP) and MSA-P) by comparing the percentage of cognitive changes between the first and the second evaluation in PD, PSP and MSA-P. The authors found a greater cognitive deterioration in patients with PSP compared with patients with MSA-P or PD and a greater cognitive worsening at follow-up in patients with MSA-P. Another longitudinal study [11] revealed a significant worsening in attention tests in 10

patients affected by MSA after a mean of 16 months, suggesting a selective deficit of attention which can occur especially along the course of the disease. No comparison between neuropsychological changes of patients with MSA-P and MSA-C was performed in the abovementioned longitudinal studies.

Recently, Fiorenzato et al. [12] reported no cognitive change in MSA-P and MSA-C between baseline and follow-up (after 15 months), however, these results should be considered cautiously due to small sample size of the patient groups (7 patients with MSA-P and 3 patients with MSA-C). Thus, the cognitive evolution associated with MSA-P and MSA-C should be better investigated in ad-hoc follow-up studies.

As regards neuropsychiatric aspects in MSA, depression occurs with a prevalence of 40–86% [5,[13], [14], [15], [16]], but also apathy is a very common symptom [17]. Until now, no longitudinal study has explored the evolution of neuropsychiatric disturbances (depression, apathy and its subtypes) in MSA and in the two different motor subtypes.

Taking into account the abovementioned background, we performed a 1-year follow-up study aimed at evaluating the evolution of cognitive and neuropsychiatric profile in patients with MSA-C and MSA-P. Since a previous study [8] reported that patients with MSA-P showed more severe and more widespread cognitive dysfunctions than patients with MSA-C, we hypothesized that (i) patients with MSA-P could have greater cognitive decline over time than MSA-C ones, and (ii) that behavioural features could be differently affected in the two MSA subtypes.

1.3 Material and methods

Subjects

Outpatients with a diagnosis of MSA according to current clinical criteria were enrolled [2].

The diagnosis of MSA and its motor subtypes was performed by a neurologist (MTP) neurologists with a 20-years expertise in diagnosing and treating multiple system atrophy. To be included patients with MSA had to be free from additional diseases that could affect cognitive performance. Patients with unintelligible speech were excluded from the study.

Age- and education-matched volunteers were recruited as control subjects (HCs) for neuropsychological tests. To be enrolled, the subjects should not have any history of head injury, or neurological, psychiatric, or physical illness that could affect cognition.

Clinical and neuropsychological assessments

Demographic and clinical aspects (disease duration; levodopa equivalent daily dose, LEDD; Unified Multiple System Atrophy Rating Scale score, UMSARS) were collected.

At baseline evaluation (T0), patients with MSA-P and MSA-C and HCs underwent a comprehensive neuropsychological battery consisting of the Italian version of the Montreal Cognitive Assessment (MoCA) and cognitive tests to assess: i. Verbal long-term memory by immediate and delayed recall of the Rey's auditory 15-word learning test and Brief Story test; ii. Attention by the brief version of the Stroop Color-Word Test (SCWT) and part A of the Trail Making Test (TMT-A); iii. Executive functions by Clock Drawing Test, immediate copying test of Rey-Osterrieth complex figure test (ROCF), phonological fluency test, and part B and index B-A of the Trail Making Test (TMT-B and TMT: B-A); iv. language by semantic fluency task, auditory comprehension task, words, non-words and sentences Repetition tasks); visuospatial perceptual and constructional functions by Benton Judgment of Lines Orientation Task, and Constructional Apraxia Task (CAT). Functional autonomy in Activity of Daily Living (ADL) and Instrumental ADL (IADL) was evaluated by specific structured interviews to patients' caregivers. Supplementaryy Material 1 reports references of cognitive tests.

Patients and HCs completed the Italian version of the Beck Depression Inventory-II (BDI-II) and Apathy Evaluation Scale (AES) to evaluate depressive symptomatology and apathy.

After 1 year (T1), all MSA patients were invited to undergo the same neuropsychological battery performed at T0.

Dementia associated with PD (PDD) was diagnosed according to PDD criteria, useful to identify dementia also in MSA [18].

Mild Cognitive Impairment associated with PD (PD-MCI) was diagnosed according to PD-MCI Level II (comprehensive assessment) criteria [19], requiring

formal neuropsychological testing with at least two tests in each of the five cognitive domains: Attention/Working memory (evaluated by the brief version of the SCWT (i.e. Time interference score) and TMT-A); Executive function (evaluated by Clock Drawing Test, immediate copying test of ROCF, phonological fluency test, TMT:B-A), Language (evaluated by semantic fluency task, auditory comprehension task, words, non-words and sentences Repetition tasks), Memory (evaluated by immediate and delayed recall of the Rey's auditory 15-word learning test and Brief Story test), Visuospatial function(evaluated by BJLOT and CAT). PD-MCI occurred when the impairment was showed on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains. Since the Level II criteria do not specify an exact cutoff for impairment on neuropsychological tests, we utilized the 1.5 SD cutoff to define impairment in this study.

Written informed consent was received from both patients with MSA and HC. The present study was reviewed and approved by the appropriate Local Ethics Committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

1.4 Statistical analysis

Cognitive and neuropsychiatric comparisons at T0 among MSA-P, MSA-C and HCs were performed by Kruskal-Wallis tests, with Dunn's test as post-hoc analysis. To compare clinical features and neuropsychological raw scores at T0 and T1 between MSA-P and MSA-C groups, Mann-Whitney *U* test or Chi-square test were employed, as appropriate.

To investigate any cognitive and neuropsychiatric changes from baseline to follow-up within MSA-C and MSA-P groups, we employed Wilcoxon signed-rank test. Finally, we applied repeated measures multivariate analysis of variance (MANOVA) to explore the interaction between the groups and the time. To control for a possible effect of depression score on cognitive variables included depression as covariate in Repeated measures MANOVA. To evaluate the possible effect of the severity of motor symptoms at T1 on the performance in cognitive tasks requiring a motor response at T1, we performed a linear regression analysis with

UMSARS-part I and II as independent variables and score on cognitive tasks requiring a motor response as dependent variables.

All statistical analyses were performed by SPSS-20 (SPSS Inc., Chicago, IL).

1.5 Results

Subjects

Twenty-nine patients with MSA-P and 21 patients with MSA-C and 30 HCs, with demographic features very similar to patients with MSA-P and MSA-C, were enrolled. The three groups did not differ on age, gender, education and MoCA score. The patients groups did not differ on disease duration, but significantly differed on LEDD and severity of motor symptoms (Table 1).

Neuropsychological comparisons at T0

Cognition. Significant differences among MSA-P, MSA-C and HCs were found on CAT, phonological and semantic fluency task, immediate and delayed copy of ROCF, all tasks of TMT, all repetition tasks. The three groups did not differ on the remaining cognitive tests assessing memory and visuospatial functions (**Table 2**).

The Dunn's test revealed that: i. MSA-P and MSA-C patients achieved poorer performance than HCs on phonological fluency task, immediate and delayed copy of ROCF, all tasks of TMT, all repetition tasks; ii. MSA-P but not MSA-C performed worse than HC on semantic fluency task; iii. MSA-C and MSA-P groups did not differ on any cognitive tests. Repeated measures MANOVA showed no significant main effect of the time (Wilks' Lambda = 0.030, F = 3.637, P = 0.237) and of the groups (Wilks' Lambda = 0.096, F = 1.049, P = 0.596) and no significant interaction between the time and groups (Wilks' Lambda = 0.074, F = 1.399, P = 0.497). In detail, MANOVA revealed a significant effect of time on CA (F = 8.798, p = 0.008), copy of ROCF (F = 16.261, p = 0.001), repetition word task (F = 4.858, p = 0.040). No significant effect of groups or interaction between time and groups was found on any cognitive variable.

The repeated measures MANOVA with depression as covariate revealed that, as for between groups, depression did not influence cognitive scores (Wilks' Lambda = 0.214; F = 0.735; p = 0.707) and, as for within subjects, the interaction

between time and depression was not statistically significant (Wilks' Lambda = 0.246; F = 0.614; p = 0.775).

Functional autonomy. Significant differences among MSA-P, MSA-C and HCs were found on ADL and IADL (Table 2). The Dunn's test revealed that both MSA-P and MSA-C patients showed a lower number of preserved ADL and IADL than HCs, but no significant difference was revealed between the two patients groups on both scale.

Neuropsychiatric parameters. Out of 50 patients with MSA, 4 patients did not complete BDI-II, and 2 patients did not perform AES and BDI-II due to marked fatigue. Significant differences among three groups on BDI-II and AES (Table 2): MSA-P and MSA-C groups had higher scores than HCs on BDI-II and AES, whereas both MSA-P and MSA-C groups had a similar score on both scales.

As for neuropsychiatric features, taking into account the cut-off scores of both BDI-II and AES, we identified 25% of patients without apathy and depression, 12.5% of patients with apathy alone, 25% of patients with depression alone, 37.5% of patients with depression and apathy within MSA-P group. Moreover, within MSA-C group, we found that 45% of patients were without depression and apathy, 5% of patients were with apathy alone, 20% of patients were with depression alone and 30% of patients were with both depression and apathy.

Neuropsychological comparisons at T1

At T1, 21/50 (42%) MSA patients participated to follow-up assessment, whereas 29/50 patients were unable to come to follow-up evaluation, mainly due to severe motor impairments. At T0, patients lost to follow-up were older and more depressed, and less educated and autonomous than patients re-evaluated at T1. Moreover, patients who were lost to follow-up had more severe motor symptoms and performed worse than re-evaluated patients on MoCA, cognitive tests assessing verbal long-term memory, visuospatial abilities, attentive and executive tests (*Supplemental Table 1*).

Out of 21 patients with MSA, 10 patients belonged to MSA-P group and 11 patients belonged to MSA-C group. These two groups did not differ on clinical, cognitive and neuropsychiatric features at both evaluations (**Table 3).** Within MSA-C, a significant increase of severity of motor symptoms evaluated by

part I and II of the UMSARS was found; moreover, a significant decline of performance on immediate copy task of ROCF and TMT-A was observed. No significant changes were found on the other neuropsychological, clinical, and functional autonomy scales (**Table 3**).

To evaluate the possible effect of the severity of motor symptoms at T1 on the performance in cognitive tasks requiring a motor response (i.e. ROCF, TMT-A) at T1, we performed a linear regression analysis with UMSARS-part I and II as independent variables and score on TMT-A and ROCF as dependent variables. We found no effect of motor symptoms on cognitive performance (*Supplementaryy Table 2*).

Taking into account cut-off score of BDI-II and AES, 7 patients were without both apathy and depression, 2 patients had apathy alone, 2 patients had both apathy and depression, none had depression alone. The proportion of depression or apathy between the baseline visit and the follow-up visit was calculated only within distinct subgroups of patients who were evaluated both T0 and T1 (MSA-C = 11). Although the overall proportion of patients assigned to the four groups at T1 did not differ from that at T0 (chi-square = 9.014, p = 0.173), an increased prevalence of apathy (from 9 to 18.2%), a relatively consistent proportion of patients without depression and apathy (63.6%), and a reduction of prevalence of pure depression (from 18.1 to 0%) were found.

Within MSA-P, a significant increase of LEDD and score on part I of UMSARS and a significant decline of performance on prose memory task, CAT, immediate copy task of ROCF, words repetition task was found. No significant change was found on the other neuropsychological, clinical, and functional autonomy scales (**Table 3**).

A linear regression with score on UMSARS-part I and II at T1 as independent variables and cognitive performance on CAT and ROCF at T1 as dependent variables revealed no effect of the severity of motor symptoms on the performance in cognitive tasks requiring a motor response (*Supplementaryy Table 2*).

Taking into account cut-off score of BDI-II and AES, at T1, 4 patients remained without both depression and apathy, 2 patient had apathy alone, 3 patients had depression alone and 1 patient remained with both depression and apathy. The proportion of depression or apathy between the baseline visit and the follow-up

visit was calculated only within distinct subgroups of patients who were evaluated both T0 and T1 (MSA-P, N = 10). The overall proportion of patients assigned to the four groups at T1 did not differ from that at T0 (chi-square = 15.276, p = 0.084), with an increase of the proportion of patients with apathy (from 10 to 20%), and of and a relatively constant proportion of patients with only depression (30%) and without apathy or depression prevalence of depression (20%).

Dementia and MCI at T0 and T1

According to diagnostic criteria for dementia no patient with MSA was affected by dementia at T0. According to clinical criteria for PD-MCI [17], we identified PD-MCI in 33/50 patients (66%) at T0; out of these, 13/21 (61.9%) patients belonged to MSA-C group and 20/29 (68.9%) patients belonged to MSA-P. At T1, out of 11 patients belonging to MSA-C group, 5 patients (45.5%) remained cognitively intact at T1 and 6 patients (54.5%) had PD-MCI at both evaluations (Chi-square = 7.336, p = 0.007). Out of 10 re-evaluated patients belonging to MSA-P group, 5 patients remained cognitively intact at T1 (50%), 2 patients (20%) developed PD-MCI at T1 and 3 patients (30%) had MCI at both evaluations (Chi-square = 1.905, p = 0.168).

1.6 Discussion

The present 1 year-follow-up study aimed at elucidating the evolution of cognitive and neuropsychiatric dysfunctions in MSA-P and MSA-C. At T0, no patient with MSA was affected by dementia, whereas 66% of the whole MSA sample had a diagnosis of PD-MCI. Moreover, patients with MSA-P and MSA-C were more depressed and apathetic and had more severe impairment of cognitive flexibility, spatial planning, set-shifting, inhibitory control and repetition abilities than HCs. The comparison between MSA-P and MSA-C revealed no significant difference on any cognitive tests and neuropsychiatric scales. At T1, a significant worsening in cognitive tests assessing spatial planning and psychomotor speed in MSA-C and a significant worsening in prose memory, spatial planning, repetition abilities and functional autonomy in MSA-P was found. The cognitive decline occurred in both groups but the cognitive evolution seems to not be the same between the groups. Although no neuropsychiatric worsening (in term of severity of depression and

apathy) was observed in MSA-P and MSA-C, an increased prevalence of apathy was found in both subtypes, whereas the prevalence of depression was reduced in MSA-C and was relatively consistent in MSA-P.

Although some studies have reported the occurrence of dementia in a low percentage of patients with MSA [20,21], in our study, no patient was affected by dementia, confirming the notion that dementia is a nonsupporting feature of MSA, as described in current diagnostic criteria [2]. On the contrary, we found a high prevalence of PD-MCI in our MSA sample with a rate prevalence very similar to that reported in Fiorenzato et al. [12].

In our study, the comparison between MSA-C, MSA-P and HCs on cognitive measures at T0 revealed deficit of cognitive flexibility, spatial planning, set-shifting, inhibitory control and repetition abilities in patients with MSA-C and MSA-P than in HCs. These findings indicate that, independently from the motor subtype of MSA, impairment of executive functions and attention abilities are distinctive cognitive hallmarks of MSA consistently with previous studies [8,[22], [23], [24], [25]] and support that cognitive deficits are integral part of the disease [3].

At T1, although cognitive status (MCI or intact cognition) remained stable after 1 year, patients with MSA-C showed a significant cognitive decline on spatial planning and psychomotor speed (evaluated by TMT-A), whereas patients with MSA-P revealed a significant decline on several cognitive functions such as spatial planning, constructional functions, prose memory and repetition abilities, independently from severity of motor symptoms. The present results diverged from those of Fiorenzato et al. [12], where no cognitive changes in MSA-P and MSA-C between T0 and T1 were found. However, the discrepancy between their findings and ours might reflect a different sample size: Fiorenzato et al. [12], in fact, included only 7 patients in MSA-P group and 3 patients in MSA-C group. Our study cannot be compared with other two studies [10,11] since they did not evaluate cognitive changes in the two subtypes of MSA.

Our finding of a wide-ranging worsening of cognitive functions and everyday functioning in MSA-P as compared to MSA-C might suggest indirectly that frontal, temporal and parietal cortex may be impaired in MSA-P more than in MSA-C [8]. On the other hand, since processing speed is mediated by cerebellum having a role

in facilitating rapid cognitive performances, our finding of a significant decline of processing speed only in patients with MSA-C might suggest indirectly the involvement of altered cerebello-cortical circuits in cognitive decline in MSA-C [8].

As for neuropsychiatric aspects, at T0, both MSA-P and MSA-C showed more severe apathy and depression when compared to HCs. Our results strengthened the evidence that besides depression, apathy occurs more frequently in MSA patients than in general population. Whereas most studies focused on depression by comparing patients with MSA to HCs or other parkinsonian syndromes [15,26,27], a very few studies have investigated apathy in MSA using tools not validated for parkinsonian syndromes [5,28], or not developed for measuring apathy as primary behavioural disturbance [29]. Until now, only one study [17] employed Apathy Evaluation Scale, a tool specific for apathy, reporting apathy in 35.7% of MSA sample without any classification of the disease according to the two motor subtypes. Unlike other previous studies, we applied simultaneously cut-off scores of BDI and AES to explore the prevalence of "pure depression" and "pure apathy" in MSA-C and MSA-P at both evaluations. At T0, prevalence of "pure depression" was similar between MSA-P and MSA-C, whereas prevalence of "pure apathy" was higher in MSA-P. This finding suggests that depression rather than apathy is the most frequent neuropsychiatric symptom in both motor subtypes of MSA. However, after 1 year, we observed an increase of prevalence of apathy in MSA-C and in MSA-P, whereas the prevalence of depression was reduced in MSA-C and remained stable in MSA-P. These finding of an increased prevalence of apathy over the course of MSA, independently from motor subtype, might suggest the idea that cognitive and neuropsychiatric dysfunctions in MSA are a consequence of a striato-frontal deafferentation, since apathy rather than depression is strongly related to damage of prefrontal-basal ganglia circuitries and thus is an executive dysfunction as demonstrated in other neurological diseases as PD [30,31].

The present study is characterized by some limitations: the first was represented by drop-out rate of about 50% of MSA sample due to severe motor deficits shown even at T0. Although this value is high, it is close to that reported in a previous study [10]. The finding could suggest the clinical relevance of teleneuropsychological assessments in MSA patients with severe motor disability

to evaluate their cognitive status at a distance in order to improve tailored cognitive treatment strategies. In the study, we could not employ alternate forms of the cognitive tests due to unavailability of the Italian versions; moreover, we could not calculate the reliable change index due to the unavailability of the standard deviation from normative sample and coefficient alpha for each cognitive test used in the study. Another limitation of the study may be the non-application of the Bonferroni adjustment; however, since our study is an exploratory research, a strict adjustment for multiple comparisons is less critical but subsequent studies with preplanned hypotheses should be conducted to confirm our findings [32].

In conclusion, our follow-up study revealed a wide-ranging worsening of cognitive functions in MSA-P as compared to MSA-C group, suggesting indirectly that frontal, temporal and parietal cortex involvement may be responsible for progression of cognitive dysfunctions in patients with MSA-P [33]. A significant decline of processing speed found only in MSA-C indirectly suggest an involvement of altered cerebello-cortical circuits in cognitive decline of MSA-C [34]. These issues should be explored by further neuroimaging studies. Moreover, these results underline the relevance of evaluating cognitive and psychiatric features of MSA in the daily clinical practice.

Table 1. Comparisons between MSA-P, MSA-C and healthy subjects.

Clinical features	***MSA-P* (n = 29)**	***MSA-C* (n = 21)**	***HCs* (n = 30)**	**Kruskal-Wallis test**	**P**
Age	62.3 ± 8.1	60.8 ± 7.8	59.9 ± 8.1	1.967	0.374
Education	10.4 ± 4.9	9.9 ± 4.6	11.3 ± 4.3	1.530	0.465
Gender (M/F)	15/14	11/10	15/15	0.032	0.984
MoCA total score	20.4 ± 4.4	21.7 ± 3.4	22.9 ± 2.9	5.029	0.081
			–	**Mann-Whitney *U* test**	
Disease duration	5.36 ± 3	4.8 ± 3	–	259.5	0.482
UMSARS-part I	26.7 ± 9.1	20.2 ± 6.8	–	136.5	0.015

UMSARS-part II	27.6 ± 7.8	21.3 ± 6.2	–	127.0	0.005
UMSARS-part IV	3.2 ± 0.9	2.6 ± 0.7	–	136.5	0.029
LEDD	441.1 ± 299.1	270.5 ± 182.8	–	89.5	0.008

MSA: Multiple System Atrophy; M: males, F: Females; MoCA: Montreal Cognitive Assessment; UMSARS: Unified Multiple System Atrophy Rating Scale; LEDD: Levodopa Equivalent Daily Dose.
Statistically significant differences were reported in bold.

Table 2. Comparisons on cognitive, neuropsychiatric and functional autonomy parameters among MSA-C, MSA-P and HCs groups.

Baseline	**MSA-C (n = 21)**	**MSA-P (n = 29)**	**Healthy subjects (n = 30)**	**Kruskal-Wallis tests**	**P**
Cognitive parameters					
RAVLT-immediate recall	31.2 ± 7.1	33.6 ± 14.1	35.9 ± 9.2	4.374	0.112
RAVLT-delayed recall	6.3 ± 2.4	6.5 ± 4.5	7.7 ± 2.9	3.133	0.209
RAVLT-recognition	12.4 ± 3.7	12.3 ± 3.2	13.6 ± 2.2	5.520	0.063
Brief story recall test	10.7 ± 3	10.6 ± 5.1	11.2 ± 3.1	0.351	0.839
CAT	10.1 ± 2.4	10.8 ± 4.5	11.7 ± 1.7	6.827	0.033
BJLOT	17.1 ± 6.8	16.9 ± 6.4	20.7 ± 5.3	5.753	0.056
Phonological fluency	22.3 ± 11.1§	20.2 ± 11.8§	33.4 ± 10.8	18.609	<0.001
Semantic fluency task	31.6 ± 11.2§	28.5 ± 10.7§	38.1 ± 11.7	10.165	0.006
Clock drawing test	7.8 ± 2.3	7.6 ± 3	9.2 ± 1.4	5.639	0.060
ROCF-immediate copy	25.9 ± 7.7	25.1 ± 8.8§	32.3 ± 5	17.986	<0.001
ROCF-delayed copy	11.7 ± 6.7	12.6 ± 8.8	15.8 ± 6.6	6.706	0.035
TMT-A	77.1 ± 34.4§	134.7 ± 156.7§	45.7 ± 32.0	22.404	<0.001
TMT-B	226.1 ± 125.8§	281.4 ± 223.3§	127.7 ± 101.8	16.773	<0.001
TMT:B-A	151.7 ± 102.2§	157.1 ± 143.5§	82.1 ± 72.4	10.475	0.005
Stroop test: time	22.2 ± 19.3	24.1 ± 27.9	24.6 ± 19.2	0.275	0.871
ENPA: word repetition	8.7 ± 1.7§	8.9 ± 1.1§	9.8 ± 0.7	18.656	<0.001
ENPA: non	3.3 ± 1.4§	3.8 ± 1.1§	4.5 ± 0.8	12.344	0.002

word repetition					
ENPA-sentences repetition	2.7 ± 0.6§	2.4 ± 1.1§	3 ± 0	11.220	0.004
ENPA-oral comprehension test	13.3 ± 0.8	13.1 ± 1.6	13.6 ± 0.9	4.574	0.102
Neuropsychiatric parameters					
BDI-II	14.1 ± 8.9§	19.8 ± 9.3§	5.1 ± 5.1	33.307	<0.001
AES	35.1 ± 7.8§	36.9 ± 9.2§	27.4 ± 4.2	21.424	<0.001
Functional autonomy					
ADL	4.8 ± 1.4§	3.2 ± 2.3§	5.9 ± 0.3	28.668	<0.001
IADL	4.6 ± 1.8§	3.6 ± 2.5§	7.3 ± 1.4	33.336	<0.001

HCs: Healthy Subjects; MSA: Multiple System Atrophy; MSA-C: Multiple System Atrophy-cerebellar subtype, MSA-P: Multiple System Atrophy-parkinsonian subtype; UMSARS: Unified Multiple System Atrophy Rating Scale; LEDD: Levodopa Equivalent Daily Dose; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; CAT: Constructional Apraxia Test; BJLOT: Benton Judgement of Line Orientation Test; ROCF: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; ENPA: Esame Neuropsicologico per l'Afasia; BDI: Beck Depression Inventory; AES: Apathy Evaluation Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living.
§ significant difference from Healthy Subjects (Dunn's test).
Statistically significant differences were reported in bold.

Table 3. Comparisons between MSA-C and MSA-P on cognitive, neuropsychiatric and functional autonomy scales at baseline and follow-up assessments.

	Time	**MSA-C (n = 11)**	**MSA-P (n = 10)**	**Mann-Whitney *U* test (p)**	**P**
Age	**T0**	58.0 ± 4.6	59.5 ± 7.7	45.5	0.512
Education	**T0**	10.7 ± 4.4	12.5 ± 4.4	45.0	0.512
Disease duration	**T0**	4.6 ± 1.8	6 ± 2.7	39.5	0.282
UMSARS-part I	**T0**	19.5 ± 4.6	21.2 ± 7.7	47.5	0.605
	T1	23.3 ± 4.7	23.3 ± 7.1	47.5	0.853
	Wilcoxon signed-rank test (p)	−2.047 (0.041)	−2.047 (0.041)		
UMSARS-part II	**T0**	21.7 ± 5.2	23.2 ± 7.8	47.5	0.605
	T1	25.4 ± 4.5	24.7 ± 8.2	46.5	0.796

	Wilcoxon signed-rank test (p)	−1.997 (0.046)	−0.954 (0.340)		
UMSARS-part IV	**T0**	2.5 ± 0.5	2.9 ± 0.9	40.0	0.481
	T1	3.1 ± 0.6	3 ± 1.1	47.5	0.853
	Wilcoxon signed-rank test (p)	−1.633 (0.102)	−1.0 (0.317)		
LEDD	**T0**	313.4 ± 190.4	366.9 ± 106.7	22.0	0.200
	T1	533.1 ± 359.1	737.1 ± 290.5	17.0	0.232
	Wilcoxon signed-rank test (p)	−1.214 (0.225)	−2.240 (0.025)		
MoCA	**T0**	21.6 ± 3.8	22.9 ± 3.5	42.0	0.387
	T1	20.0 ± 2.7	21.6 ± 4.9	41.5	0.349
	Wilcoxon signed-rank test (p)	−1.447 (0.148)	−1.080 (0.280)		
RAVLT-immediate recall	**T0**	34.7 ± 5.1	40.8 ± 16.5	52.0	0.863
	T1	32.2 ± 10.2	38.8 ± 17.8	44.5	0.468
	Wilcoxon signed-rank test (p)	−0.802 (0.423)	−0.564 (0.573)		
RAVLT-delayed recall	**T0**	7.1 ± 2.8	8.4 ± 4.2	55.0	1
	T1	8 ± 2.3	9.3 ± 3.4	42.5	0.387
	Wilcoxon signed-rank test (p)	−0.772 (0.440)	−1.199 (0.230)		
RAVLT-recognition	**T0**	12.8 ± 4.3	13.6 ± 1.7	52.5	0.863
	T1	12.8 ± 4.4	13.3 ± 3	53.5	0.918
	Wilcoxon signed-rank test (p)	0 (1)	−0.137 (0.891)		
Brief story recall test	**T0**	11 ± 3.2	11.8 ± 2	48.0	0.654
	T1	11.4 ± 2.4	9.6 ± 3.7	39.5	0.282
	Wilcoxon	−0.359 (0.719)	−2.098 (0.036)		

	signed-rank test (p)				
CAT	**T0**	11.1 ± 2.1	11.9 ± 2.1	42.5	0.387
	T1	10.2 ± 2.1	10.2 ± 2.5	52.5	0.863
	Wilcoxon signed-rank test (p)	−1.328 (0.184)	−2.263 (0.024)		
BJLOT	**T0**	17.5 ± 7.5	21.7 ± 4.3	37.0	0.223
	T1	17.4 ± 7.2	18.2 ± 7.6	54.5	0.973
	Wilcoxon signed-rank test (p)	0 (1)	−1.605 (0.108)		
Phonological fluency	**T0**	24.4 ± 13.1	31.5 ± 14.3	38.0	0.251
	T1	23.8 ± 12.4	32.6 ± 16.6	34.5	0.152
	Wilcoxon signed-rank test (p)	−0.211 (0.833)	−0.237 (0.812)		
Semantic fluency task	**T0**	33.5 ± 14.2	33.6 ± 11.4	48.5	0.863
	T1	32.5 ± 12.1	33.4 ± 11.3	49.0	0.705
	Wilcoxon signed-rank test (p)	−0.535 (0.593)	−0534 (0.593)		
Clock drawing test	**T0**	8.1 ± 2.4	8.8 ± 2.4	43.0	0.756
	T1	6.8 ± 2.5	8.8 ± 1.3	30.0	0.085
	Wilcoxon signed-rank test (p)	−1.895 (0.058)	−0.710 (0.478)		
ROCF-immediate copy	**T0**	29.1 ± 7	30.8 ± 5.6	45.5	0.512
	T1	24.5 ± 8.1	23.6 ± 9.1	52.0	0.863
	Wilcoxon signed-rank test (p)	−2.608 (0.009)	−2.194 (0.028)		
ROCF-delayed copy	**T0**	13 ± 6.9	14.2 ± 8.5	49.0	0.705
	T1	14.9 ± 7.6	18 ± 10.9	48.0	0.654
	Wilcoxon signed-	−1.253 (0.210)	−1.187 (0.235)		

	rank test (p)				
TMT-A	**T0**	65.9 ± 25.2	68.5 ± 44.1	49.5	0.705
	T1	77.3 ± 32.6	69.6 ± 55.5	42.0	0.387
	Wilcoxon signed-rank test (p)	−2.179 (0.029)	−0.280 (0.779)		
TMT-B	**T0**	219.1 ± 107.6	190 ± 151.2	41.0	0.349
	T1	227.1 ± 126.3	205.1 ± 157.8	39.5	0.282
	Wilcoxon signed-rank test (p)	−0.178 (0.859)	−0.153 (0.878)		
TMT:B-A	**T0**	158.4 ± 90.6	121.5 ± 127.8	37.5	0.223
	T1	151.6 ± 104.2	138.5 ± 117.9	43.5	0.426
	Wilcoxon signed-rank test (p)	−0.222 (0.824)	−0.459 (0.646)		
Stroop test: time	**T0**	22.6 ± 22.6	14.1 ± 11.9	44.0	0.468
	T1	24.4 ± 10.1	23.6 ± 16.6	47.5	0.605
	Wilcoxon signed-rank test (p)	−0.489 (0.625)	−1.071 (0.284)		
ENPA: word repetition	**T0**	9 ± 1.7	9 ± 1.1	35.5	0.605
	T1	9.7 ± 0.6	9.8 ± 0.4	55.0	1
	Wilcoxon signed-rank test (p)	−1.186 (0.236)	−2.060 (0.039)		
ENPA: non word repetition	**T0**	3.8 ± 1.5	3.9 ± 0.7	42.0	0.605
	T1	3.9 ± 0.9	4.2 ± 0.8	46.0	0.557
	Wilcoxon signed-rank test (p)	−0.216 (0.829)	−1.732 (0.083)		
ENPA-sentences repetition	**T0**	2.7 ± 0.6	2.9 ± 0.3	41.0	0.756
	T1	3 ± 0	3 ± 0	55.0	1
	Wilcoxon signed-rank test	−1.342 (0.180)	−1.0 (0.317)		

	(p)				
ENPA-oral comprehension test	**T0**	13.2 ± 1	13.5 ± 0.9	29.0	0.387
	T1	13.4 ± 0.8	13.2 ± 1.2	55.0	1
	Wilcoxon signed-rank test (p)	−0.707 (0.480)	−1.134 (0.257)		
BDI-II	**T0**	12.1 ± 6.6	15.1 ± 8.4	36.0	0.331
	T1	12.55 ± 7.2	14.6 ± 10.8	51.0	0.809
	Wilcoxon signed-rank test (p)	−0.359 (0.719)	−0.119 (0.906)		
AES	**T0**	35.4 ± 7.9	31.9 ± 7.2	42.0	0.387
	T1	36.4 ± 8.4	30.4 ± 10.1	39.0	0.282
	Wilcoxon signed-rank test (p)	−0.760 (0.447)	−0.409 (0.683)		
ADL	**T0**	5.1 ± 0.8	4.7 ± 1.9	51.0	0.809
	T1	4.4 ± 1.4	3 ± 2.1	31.5	0.175
	Wilcoxon signed-rank test (p)	−1.630 (0.103)	−1.567 (0.117)		
IADL	**T0**	5.2 ± 1.6	5.3 ± 2.6	50.0	0.756
	T1	4 ± 1.8	3.3 ± 1.8	39.5	0.456
	Wilcoxon signed-rank test (p)	−1.622 (0.105)	−1.479 (0.139)		

HCs: Healthy Subjects; MSA: Multiple System Atrophy; MSA-C: Multiple System Atrophy-cerebellar subtype, MSA-P: Multiple System Atrophy-parkinsonian subtype; UMSARS: Unified Multiple System Atrophy Rating Scale; LEDD: Levodopa Equivalent Daily Dose; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; CAT: Constructional Apraxia Test; BJLOT: Benton Judgement of Line Orientation Test; ROCF: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; ENPA: Esame Neuropsicologico per l'Afasia; BDI: Beck Depression Inventory; AES: Apathy Evaluation Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living.

Statistically significant differences were reported in bold.

Wilcoxon signed-rank test was used to compare demographic, cognitive and neuropsychiatric variables at T0 and T1 within each group; Mann-Whitney *U* test (p) was used to compare MSA-P and MSA-C groups on demographic, cognitive and neuropsychiatric variables at T0 and T1.

Supplementaryy material

Supplementaryy Table 1. Comparisons between participants to follow-up assessment and patients lost to follow-up.

	Re-evaluatedpatients (n=21)	**Lost to follow-up assessment (n=29)**	**Mann-Whitney U test**	**P**
Disease duration	5.3 ± 2.3	5 ± 3.4	258.0	0.463
UMSARS-part I	20.3 ± 6.2	26.8 ± 9.5	138.0	**0.015**
UMSARS-part II	22.4 ± 6.4	26.9 ± 8.3	161.0	**0.038**
UMSARSA-part IV	2.7 ± 0.8	3.1 ± 0.9	157.0	0.094
LEDD	341.7 ± 149.4	440.6 ± 379.8	187.5	0.829
Age	58.7 ± 6.1	63.8 ± 8.4	184.0	**0.018**
Education	11.57 ± 4.4	9.2 ± 4.8	202.0	**0.041**
MoCA	22.2 ± 3.6	17.8 ± 5.6	168.5	**0.011**
RAVLT-immediate recall	37.6 ± 12.1	28.8 ± 9.8	173.0	**0.014**
RAVLT- delayedrecall	7.7 ± 3.5	5.5 ± 3.7	186.5	**0.029**
RAVLT- recognition	13.2 ± 3.3	11.7 ± 3.3	172.5	**0.019**
Brief story recall test	11.4 ± 2.7	10.1 ± 5.1	237.5	0.335
CAT	11.5 ± 2.1	9.1 ± 2.3	130.5	**<0.001**
BJLOT	19.5 ± 6.4	15.1 ± 6.1	175.5	**0.011**
Phonologicalfluency	26.6 ± 13.2	17.1 ± 7.9	154.5	**0.013**
Semanticfluency task	33.2 ± 12.8	27.4 ± 8.8	207.0	0.175
Clock drawing test	8.5 ± 2.5	7.1 ± 2.7	179.0	0.071
ROCF-immediate copy	29.9 ± 6.2	22 ± 8	115.5	**<0.001**
ROCF-delayed copy	13.6 ± 7.5	11.1 ± 8.2	223.5	0.211
TMT-A	67.1 ± 34.5	142.21 ±153.4	146.0	**0.003**
TMT-B	205.2 ± 127.6	296.9 ± 217.1	221.0	0.140
TMT:B-A	140.9 ± 108.7	165.1 ± 139.1	264.5	0.551
Stroop test: time	18.5 ± 18.4	26.9 ± 27.7	228.5	0.251
ENPA: word repetition	8.9 ± 1.5	8.7 ± 1.3	212.0	0.293
ENPA: non word repetition	3.9 ± 1.2	3.3 ± 1.2	181.0	0.082
ENPA- sentencesrepetition	2.8 ± 0.5	2.3 ± 1	189.0	0.063
ENPA-oralcomprehension test	13.4 ± 0.8	12.9 ± 1.6	222.0	0.298
BDI-II	13.4 ± 7.4	20.3 ± 10	140.0	**0.018**
AES	33.7 ± 7.6	38.1 ± 9	200.0	0.082
ADL	4.9 ± 1.4	3.1 ± 2.2	165.0	**0.005**
IADL	5.2 ± 2.1	3.2 ± 1.9	145.0	**0.002**

UMSARS: Unified Multiple System Atrophy Rating Scale; LEDD: Levodopa Equivalent Daily Dose; MoCA: Montreal Cognitive Assessment; RAVLT:Rey Auditory Verbal Learning Test; CAT: Constructional Apraxia Test; BJLOT: Benton Judgement of Line Orientation Test; ROCF: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test; ENPA:EsameNeuropsicologico per l'Afasia; BDI: Beck Depression Inventory, AES:

Apathy Evaluation Scale; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living

Supplementary table 2. Findings from regression analysis to evaluate the influence of severity of motor symptoms evaluated at follow-up evaluation (T1) on performance in cognitive tests requiring a motor response performed at T1

	Beta	**T**	**p**
MSA-C			
Immediate copy of ROCF			
UMSARS-part I	0.590	1.242	0.254
UMSARS-part II	-0.672	-1.415	0.200
TMT-A			
UMSARS-part I	-0.058	-0.115	0.912
UMSARS-part II	0.428	0.857	0.420
MSA-P			
Immediate copy of ROCF			
UMSARS-part I	-0.361	-0.532	0.611
UMSARS-part II	-0.128	-0.189	0.856
CAT			
UMSARS-part I	-0.246	-0.444	0.670
UMSARS-part II	-0.470	-0.848	0.424

MSA-C: Multiple System Atrophy-cerebellar subtype, MSA-P: Multiple System Atrophy-parkinsonian subtype; UMSARS: Unified Multiple System Atrophy Rating Scale; CAT: Constructional Apraxia Test; ROCF: Rey-Osterrieth Complex Figure Test; TMT: Trail Making Test.

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2. Effects of gender on cognitive and behavioral manifestations in Multiple System Atrophy

Published in J Neural Transm 2020 Mar 14

2.1 Abstract

Introduction. Gender differences have been described in several neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease. The effects of gender on cognitive and behavioral manifestations in Multiple System Atrophy and the changes of cognitive functions over time according to gender have not been investigated so far. Methods. Fifty-five patients with a diagnosis of Multiple System Atrophy underwent a comprehensive neuropsychological and neuropsychiatric battery at baseline and 26 of them could be re-evaluated at 1 year follow-up. Results. At baseline women with Multiple System Atrophy had poorer global cognitive state and visuo- spatial abilities, and a higher prevalence of depression and apathy than males. At follow-up, female patients deteriorated more than males on attention abilities and motor functions, and had a higher prevalence of depression than men. Executive functions and visuo-spatial abilities significantly worsened over time in both groups. Mild Cognitive Impairment single domain was significantly more frequent in females than males. Conclusions. Cognitive and behavioral differences between genders in Multiple System Atrophy involve global cognition, planning, attention, visual-perceptive skills and depression, with female patients more compromised than males. Female patients deteriorated more than men over time as for motor functions and attention. Further longitudinal studies are deserved to confirm gender differences in progression of cognitive and behavioural features of Multiple System Atrophy.

2.2 Introduction

Multiple System Atrophy (MSA) is a neurodegenerative disorder characterized by various combinations of parkinsonism, cerebellar ataxia, autonomic failure and corticospinal impairment. Cognitive impairment is a non-supporting feature for MSA diagnosis but in the past few years it has been found to be a frequent feature in MSA. Cross-sectional studies show that cognitive dysfunction may affect executive, memory, attention and visuo-spatial domains in MSA [1-2]. As regards

executive dysfunction, spatial planning is most compromised in MSA, followed by cognitive flexibility; moreover, linguistic domain can be altered too [3].Lifetime incidence of significant cognitive impairment according to DSM-IV has been reported to be 14% in a retrospective clinico-pathological study[4]**.** As regards behavioral manifestations, the combination of depression and apathy is more frequent than depression or apathy alone; 35% of MSA patients experienced both depression and apathy, 15% of patients were only depressed and 15% of them presented apathy alone [3]. In previous studies, depression occurred with a prevalence of 40-86% [2-5]. According to the available longitudinal studies, attention deteriorated during the course of the disease and a trend towards worsening of other cognitive domains was also observed in small groups of MSA-P and MSA-C [6].

According to the Institute of Medicine's Committee on Understanding the Biology of Sex and Gender Differences, sexual differences, involving genes, fetal hormones and a variety of broader social factors have important implications on brain structure and function and on the risk, course and outcome of neurodegenerative diseases [7-8]. The impact of gender on survival and clinical features of MSA, such as autonomic and motor symptoms, has been reported, but no previous study has assessed the effect of gender on cognitive manifestations of the disease. Longer survival has been reported in males-MSA compared to females in some studies, while others showed no difference in survival rates [9]. Females-MSA were more likely to initially manifest motor symptoms and receive an earlier diagnosis than males [10]. Males were more likely to have autonomic symptoms at onset, which tended to be more severe throughout the disease course [8]. While the overall survival benefit was 3.6 months in females, the difference in time from diagnosis to death was almost 1-year between sexes, therefore females had a slightly longer disease course overall than males [8].

In the perspective of gender medicine, the study of gender differences in cognition / behavior in MSA can help us better understand the profile of patients, have an additional variable to make predictions on progression and favor pharmacological and non-pharmacological treatment more targeted to the person.

This was an exploratory study aimed to investigate the effects of gender on cognitive and behavioral manifestations in MSA and to assess changes of cognitive functions over time according to gender, therefore no correction for multiple comparisons was applied.

2.3 Material and Methods

Subjects

Between November 2015 and April 2019, 55 patients with a diagnosis of MSA according to current criteria [11] were enrolled at the Center for Neurodegenerative Diseases of the University of Salerno. After 1-year, 26/55 patients participated in a follow-up assessment; out of 29 patients, 10 patients had died (M=4, F=6; p=0.294) and 19 weren't able to return to the hospital due to worsening of the disease (M=11, F=8; p=0.487).

The severity of the disease was assessed by Unified Multiple System Atrophy Rating Scale (UMSARS) [12]. Subjects with a history of head injury, other neurological, psychiatric or physical illness which may affect cognition, were excluded. The Local Ethics Committee approved the study.

Neuropsychological and neuropsychiatric assessment

Patients underwent a neuropsychological and neuropsychiatric battery at baseline (T_0) and 1-year follow-up (T_1) evaluation. Global cognitive abilities were screened with the Montreal Cognitive Assessment (MoCA). Memory domain was investigated with the delayed recall scores of the Rey Auditory Verbal Learning Test (15-RAWLT), the Prose Memory Test and the Recall of Rey Osterrieth Figure. Attention domain was explored through part-A of the Trail Making Test (TMT-A) and the short version of StroopColor-Word Test (SCWT) considering the error interference effect. Executive functions were assessed with the Clock Design Test (CDT), the Semantic Verbal Fluency Test (SVF) and the Copy of the Rey Osterrieth

Figure.Visuo-spatial functions were tested with the Constructional Apraxia Test and Benton's Judgment of Line Orientation (BJLO). Language domain was explored with two sub-tests from the Neuropsychological Examination of Aphasia battery (ENPA), the non-word repetition test and the hearing comprehension test of sentences. Functional autonomy was evaluated with the Instrumental Activities of Daily Life (IADL) and with the Basic Activities of Daily Life (ADL), while depression and apathy with, respectively, the Beck Depression Inventory II (BDI-II), using cut-off>12, and Apathy Evaluation Scale (AES), using cut-off>37 [13].

Using the z-scores of the individual tests and a control group consisting of 42 healthy participants with age and education similar to the patients, enrolled subjects were classified as having MSA with normal cognition (MSA-NC), MSA with MCI-single domain (MSA-MCIsd), MSA with MCI-multiple domain (MSA-MCImd) and MSA with dementia (MSA-D).

Due to the lack of specific MCI criteria for MSA, MDS MCI criteria for Parkinson's disease were applied [14]. As such, MCI was defined as an impairment in at least 2 neuropsychological tests (score below 1.5 standard deviation). Patients showing impairment in one single domain were classified as MSA-MCIsd, while patients with impairment in at least two cognitive domains were classified as MSA-MCImd. Patients presenting wide-spread cognitive/behavioral decline associated with impairment of functional autonomy were considered as affected by MSA-D, according to Statistical Diagnostic Manual of Psychiatry–5th Edition (DSM-5).

Statistical analysis

Comparisons at baseline evaluation among male and female patients were performed by applying T-test for independent samples. Moreover, to analyze the impact of gender on cognitive and behavioral manifestation at T0 and T1, we used a generalized linear model-mixed design2x2 (ANOVA-mixed design2x2).

We used Chi-square analysis(χ2) or Fisher's exact test, as appropriate, to compare the percentage of normal cognition (MSA-NC), MCI-single domain (MSA-

MCIsd), MCI-multiple domain (MSA-MCImd) and dementia (MSA-D) between genders. We used $\chi 2$ or Fisher's exact test as appropriateto compare the percentage of depression, apathy and depression with apathy. Pearson's correlations were used to analyze the relationship between behavioral data, UMSARS and levodopa equivalent daily dose (LEDD).

We used Mann-Whitney's test for independent samples in order to explore the differences between females and males with MSA-P and with MSA-C; significant level was set at ≤ 0.05. Data analysis was conducted with SPSS (Version 23.0).

2.4 Results

Motor, cognitive and behavioral variables in whole MSA sample

Fifty-five patients with MSA were included and divided in two groups according to gender: 52.7% (29) were men and 47.2%(26) were women.The two groups didn't differ in age, education, disease duration or LEDD. In spite of a similar disease duration, MSA females presented higher UMSARS-IV score than males (p=0.041) and a trend towards higher scores in UMSARS-I and II (**Table 1**).

At baseline, males showed better scores than females at MOCA global score (p=0.036), MOCA linguistic and attention sub-scores (p=0.008; p=0.001), Benton's Judgment of Line Orientation (BJLO) (p<0) and a trend towards better scores at Clock design test (CDT), apathy investigated by AES and basic skills of daily life assessed by ADL questionnaire. The two groups didn't differ on the remaining cognitive tests (**Table 1**).

At 1-year follow-up ANOVA-mixed design2x2 revealed significant main effect for variable between groups-Gender on MOCA attention sub-score (p=0.023), BJLO (p=0.010), CDT (p=0.020), Copy of the Rey Osterrieth figure (p=0.042), Recall of the Rey Osterrieth figure (p=0.013). It revealed significant main effect for variable within groups-Time on UMSARS-I-II and IV (p=0.007; p=0.044; p=0.027), MOCA executive functions sub-test (p=0.010), BJLO (p=0.043), Copy of the Rey Osterrieth figure (p=0.001), TMT (p=0.015), Stroop test- error effect (p=0.016), the

IADL (p=0.002), the ADL (p=0.027) and a trend towards significance on Constructional Apraxia Test (p=0.052). It revealed significant interaction effect between Gender and Time variables on UMSARS-IV (p=0.027), TMT (p=0.009) and the non-word repetition test of ENPA (p=0.028) (**Table 2**).

At baseline, according to the BDI-II, 54.2% of MSA males as compared with 72% of MSA females were depressed (*p*=0.196) (**Fig.1a**). According to AES, 39.3% of MSA males had apathy as compared with 56% of MSA females (*p*=0.224) (**Fig.1b**). Moreover, 32.1% of MSA males and 40% of MSA females had both depression and apathy (p=0.580).At baseline, there were significant positive correlations between BDI-II and UMSARS-I (r=0.450, p=0.024), UMSARS-II (r=0.458, p=0.021) and UMSARS-IV (r=0.459, p=0.021) in MSA females. There was a trend towardsa significant correlation between AES and both UMSARS-I (r=0.401, p=0.052) and UMSARS-II (r=0.385, p=0.057) in MSA males. At baseline, there was a significant negative correlation between AES and LEDD in MSA males (r=-0.017, p=0.017).

At 1-year follow-up, 16% of MSA males as compared with 57.1% of MSA females were depressed (*p*=0.051) and 27.3% of MSA males had apathy as compared with 64.3% of MSA females (*p*=0.111). Moreover,8.3% of MSA males and 35.7% of MSA females had both depression and apathy (p=0.170). At 1-year follow-up, in 9/12 males and 9/14 females, depression scores didn't change as compared to baseline, in 2 males and 3 females depression worsened and in 2 females improved (p=0.393); moreover, in 8/12 males and 9/14 females apathy scores didn't change as compared to baseline, in 2 males and 4 females apathy worsened and in 1 male and 1 female improved (p=0.831). At follow-up, in MSA-female group, there was a significant negative correlation between AES and UMSARS-I (r=-0.769, p=0.015).

Dementia and MCI

Regarding the cognitive status of the whole sample, 66% of MSA males had a normal cognitive status, 10% had MCI-sd, 24% had MCI-md and no one had dementia, whereas 50% of MSA females had a normal cognitive status, 31% had MCI-sd, 15% had MCI-md and 4% had dementia. MCI-sd was significantly more prevalent in MSA females than males (p=0.021). There were no significant

differences in the prevalence of Dementia, MCI-md and NC between genders (p=0.494; p=0.610; p= 0.377). Cognitive status according to gender is shown in **Fig.2.**

Furthermore, at follow-up 7.1% of females and 0% of males had a diagnosis of dementia (p= 0.538), MCI-sd was present in 16.7% of males and in 28.6% in females (p = 0.404), MCI-md was present in 0.0% of males and in 14.3% of females (p= 0.280), NC was present in 83.3% of males and in 50% of females (p=0.085). At 1-year follow-up, 8/12 males and 9/14 females had a cognitive status equal to the baseline, 1 male and 4 females had worsened, and 3 males and 1 female had improved.

Motor, cognitive and behavioral variables in MSA-P and MSA-C

Sixteen males and 16 females were affected by MSA-P and 13 males and 10 females by MSA-C. Among MSA-P patients there was no difference in age and education according to gender, but females had a shorter disease duration than males (p=0.044). Among MSA-C patients there was no difference in age, education and disease duration according to gender.

At baseline, MSA-P males had lower scores than females on UMSARS-I (p=0.041), UMSARS-II (p=0.005), UMSARS-IV (p=0.015) and apathy investigated by AES (p=0.046). They had higher scores than females on MOCA global score (p=0.018), MOCA attention sub-score(p=0.002) and Benton's Judgment of Line Orientation (BJLO) (p=0.001). There was a trend towards significance on Clock design test (CDT) with better scores in males (p=0.058) and on Stroop test-error interference with better scores in females (p=0.058). Intra-group gender differences couldn't be assessed at follow-up due to the small sample.

At baseline significant differences between genders in MSA-C were found on MOCA linguistic sub-score(p=0.023) and non-word repetition test of ENPA (p=0.025), with males having better scores than females in MOCA linguistic sub-score and females showing better scores than males in sub-test of ENPA. The two groups didn't differ in the remaining cognitive tests.

2.5 Discussion

The aim of this paper is to explore gender differences in MSA regarding cognitive and behavioral manifestations.

In our study, female patients had a greater motor disability than male patients in spite of a similar age and disease duration [4].Our findings are consistent with a previous study [8] which assessed clinical features of 685 MSA patients, without using UMSARS, and found significant differences in symptoms at onset, that were more frequently only motor in females (236 patients, 72%) compared to males (213 patients, 60%), while autonomic-only symptoms were more common in males (116 patients, 33%) compared to females (70 patients, 21%). As for motor disability, falls early in the disease course were also more common in female than male patients.

As for the cognitive variables, at baseline women had a lower score on the MOCA global score test and the subcomponents investigating language and attention and a worse performance at the Benton's Judgment of Line Orientation (BJLO), investigating visuo-spatial abilities. The finding of a worse global cognitive state in female patients with MSA as compared to males differs from what is known about PD, where women generally perform better than men [15-16] but is consistent with other neurodegenerative disorders, such as Alzheimer's disease (AD), where women are significantly more impaired than men. In fact, a meta-analysis of cognitive findings from 15 studies on AD showed a consistent male advantage in verbal and visuo-spatial tasks and tests exploring episodic and semantic memory [17]. In addition, Gale and colleagues (2016) [18] underlined a greater worsening of verbal and visuo-spatial performance in females with both MCI and AD as compared to males. Moreover, healthy elderly women showed significantly faster age-related decline and greater cognitive deterioration than elderly men [19]. It has been hypothesized that such differences can be related to cognitive reserve, but this hypothesis cannot account for the differences per se, since some studies show that gender differences persist in spite of a similar cognitive reserve, suggesting that difference in sex may be task-specific, rather than domain-specific [20].

Aworse performance in visuo-spatial test has not been previously reported in MSA females but is in line with the data reported in Parkinson Disease (PD) [21]. In a previous study, we found that29% of MSA patients had linguistic deficits as assessed by semantic fluency task, auditory comprehension task, words, non-words and sentence repetition tasks [3] even if most previous studies only investigated the motor speech abilities of MSA patients because dysarthria represents an early and prominent clinical feature of MSA, and objective speech assessment may provide an inexpensive and widely applicable screening instrument for differentiation of MSA and PD [22]. Indeed, our findings suggest that it could be useful to evaluate MSA patients with a specific neuropsychological language battery in order to better study comprehension, naming abilities, writing and semi-spontaneous speech.

At follow-up, we found that female patients deteriorated over time more than men on attention abilities and motor function, while executive functions and visuo-spatial abilities significantly worsened over time in both groups.

In conclusion, we found that cognitive differences between genders involve global cognition as assessed by MOCA, planning assessed by Copy of the Rey Osterrieth figureand, more specifically, attention and visual-perceptive skills, were more compromised in female patients. Moreover, we found that female patients deteriorated more than men over time for motor function and attention.

The concept of MCI in MSA has been proposed in a few previous studies*[23-24]*, suggesting that MSA patients may present a wide spectrum of cognitive changes that range from mild single domain deficits to multiple domain impairment and, more rarely, to dementia, with cognitive decline most frequently characterized by frontal-executive dysfunction [25-26]. In our study, we found that MCI-sd was significantly more frequent in females than males and that the majority of patients, both males and females, had NC. In agreement with the literature, dementia was poorly represented in both genders. However, we observed that female patients tended to have a worse cognitive status than males at follow-up, even if the difference was not significant, likely due to the small sample size.

By assessing gender differences in MSA-P and MSA-C subtypes at baseline, we found that females with MSA-P diagnosis had worse scores than males on UMSARS (I-II-IV), MOCA-global score test and the CDT, both investigating the global cognitive state, BJLO and Stroop test-effect error, exploring visuo-perceptual abilities and inhibitor control. In MSA-C, differences between males and females on linguistic functions are inconsistent and need to be further studied with a more detailed battery.

As regards behavioral features, we have mainly studied depressive and apathetic symptoms. In our baseline study there was a higher prevalence of depression and apathy in females than in males, but the difference was not significant, probably due to the small sample. In a preliminary report on 175 patients with MSA (51.4% male), depression occurred more frequently in women than in men ($p = 0.04$) [27]. Our results are also in line with other data collected in PD, in which a history of depression is more frequently reported in women than in males. In PD, a study performed on elderly women with PD found a reduced risk of apathy compared to men with PD however; this finding is not in line with our results in MSA patients that were not necessarily elderly [28-29]. Regardless of the relationship between apathy and reduced levels of striatal-dopamine transporter, also confirmed by the efficacy of some dopaminergic drugs on apathetic symptoms, in our study, we found that LEDD had a significant negative correlation with apathy only in males [30 -31].

We also found that at follow-up women had a higher prevalence of depression than men (57,1 vs 16%; $p=0.051$) and a higher not significant prevalence of apathy and co-occurrence of depression and apathy. At follow-up, apathy seemed to worsen more commonly in women (4/14) than men (2/12), but we recognize that the small sample at follow-up probably affected the results of our study. Indeed, both disease progression preventing patients from returning to follow-up and death could be expected in a rapidly progressive disease such as MSA, however no differences in percentage of deaths or patients unable to return to follow-up were observed between genders. Further larger longitudinal studies are deserved to confirm gender differences in progression of cognitive and behavioral features of MSA.

Fig. 1: Fig. 1a Patients with clinically significant depression according to sub-groups. Patients with BDI-II score greater than 12. **Fig. 1b**Patients with clinically significant apathy according to sub-groups. Patients with AES score greater than 37.

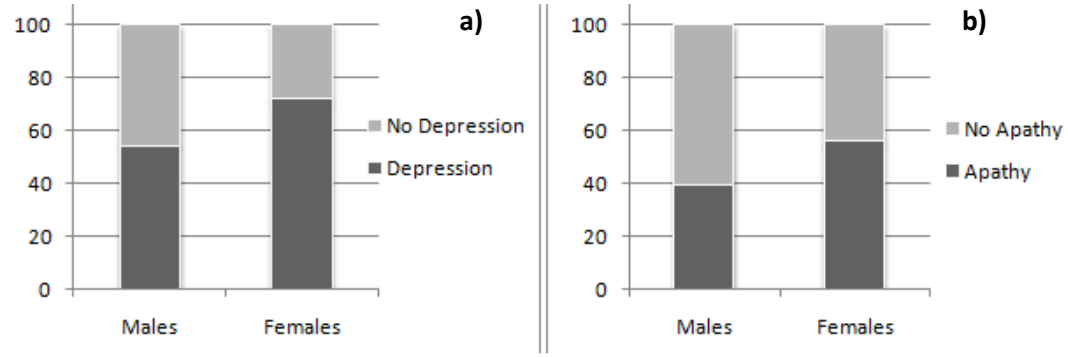
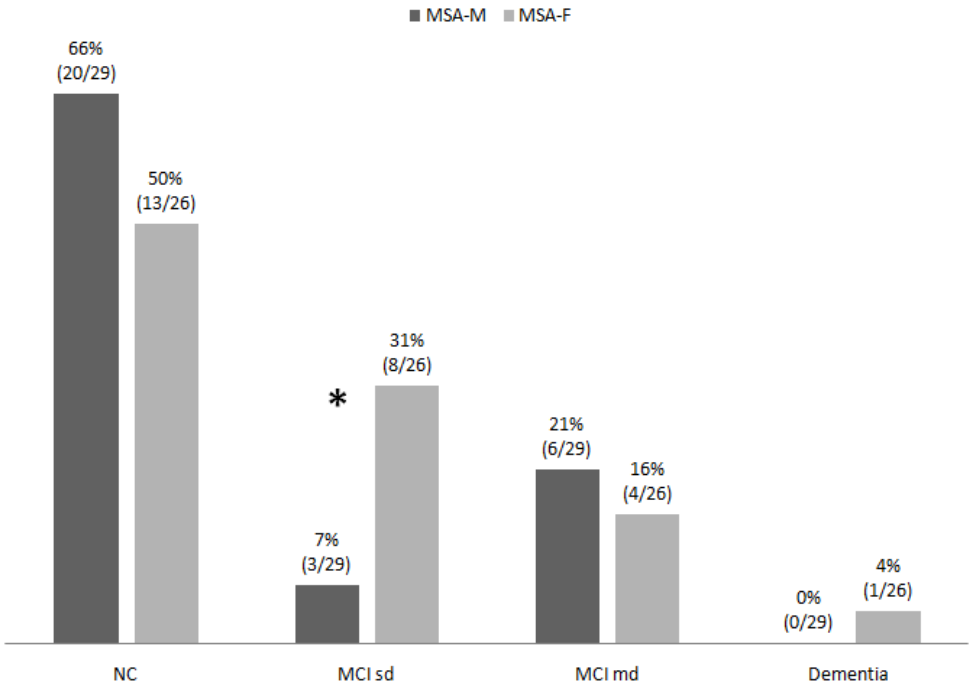


Fig. 2: Cognitive status according to phenotype in groups of MSA-male and MSA-females.



* Statistically significant differences
F: females; M: males; MSA: multiple system atrophy*; D:* dementia, *NC:* normal cognition; *MCI-md:* mild cognitive impairment multiple domain; *MCI-sd:* mild cognitive impairment single domain.

Tab.1: Demographic/clinical features, neuropsychological and behavioral features of MSA-males and MSA-females at baseline.

	MSA-M (N:29)	**MSA-F (N:26)**	**T**	**P**
Demographic/clinical features				
Age	61.79±8.43	62.57 ±7.51	-0.362	0.719
Education	10.34±4.76	9.53 ± 4.86	0.627	0.538
Disease duration	5.59 ± 3.03	4.62 ± 3.04	1.183	0.242
UMSARS I	21.54±8.81	25.8 ± 8.32	-1.75	0.085
UMSARS II	22.92±6.85	26.96±8.07	-1.92	*0.060*
UMSARS IV	2.65±0.93	3.20±0.86	-2.10	0.041
LEDD	431.72±365.44	361.85±224.64	0.719	0.477
Cognitive Assessments				
MOCA global score[§]	20.72±4.12	17.72±6.05	2.15	0.036
- Visuospatial	2.82±1.25	2.40±1.32	1.21	0.229
- Executive	1.62±1.26	1.24±1.42	1.04	0.303
- Language	4.44±0.90	3.60±1.22	2.78	0.008
- Orientation	5.51±0.87	5.44±0.86	0.32	0.746
- Attention	5.24±1.02	3.72±2.03	3.54	0.001
- Memory	1.25±1.45	1.32±1.46	-0.17	0.862
Memory domain	31.20±11.32	32.60±11.67	-0.44	0.659
- 15-RAWLT[§]	10.49±3.64	10.43±5.07	0.050	0.969
- Prose memory[§]	12.87±8.21	10.74±7.23	0.998	0.323
- Recall of Rey Osterrieth figure				
Attention domain	98.00±84.68	126.4±148.3	-0.879	0.383
- TMT-part A[§]	14.54±18.66	9.72±12.26	1.097	0.278
- Stroop test- error interference[§]				
Executive domain	8.22±2.30	6.75±3.17	1.907	*0.062*
- CDT§	30.85±10.40	27.80±11.18	1.019	0.313
- SVF§	25.75±8.92	23.32±8.62	1.005	0.320
- Copy of the Rey Osterrieth figure				
Visuospatial domain	10.21±2.83	10.24±4.74	-0.024	0.981
	19.65±4.77	13.61±6.53	3.943	0.000
- Constructional apraxia test[§]				
- BJLO[§]				
Language domain	3.29±1.35	3.83±1.04	-1.56	0.123
- ENPA-non word repetition[§]	13.38±0.85	12.96±1.58	1.198	0.237
- ENPA-auditory comprehension of sentences[§]				

Behavioral Assessments				
- *BDI-II*	16.41±9.81	18.80±10.76	*-0.836*	0.407
- *AES*	35.35±8.32	39.68±9.19	*-1.797*	*0.078*
Functional autonomy				
- ADL	4.31±1.92	3.23±2.25	1.915	*0.061*
- *IADL*[§]	3.96±2.19	4.12±2.40	-0.247	0.807

Values are shown in mean± standard deviation

Statistically significant differences are indicated in bold

[§]tests used to identify NC, MCI and Dementia (Litvan et al., 2012); 15-RAWLT: Rey'sauditory 15-word learning test; ADL: Based Activities of Daily Life; AES: Apathy Evaluation Scale; BDI-II: Beck Depression Inventory II; BJLO: Benton'sJudgment of Line Orientation; CDT: Clock Drawing test; ENPA: Neuropsychological Examination of Aphasia battery; F: females; IADL: Instrumental Activities of Daily Life; LEDD:levodopa equivalent daily dose; M: males; MCI: Mild Cognitive Impairment; MoCA: Montreal Cognitive Assessment battery; MSA: multiple system atrophy; p= p-value; SPSS: Statistical Package for Social Science; SVP: Semantic Verbal Fluency; t: T Test;TMT: Trial Making Test; UMSARS:Unified Multiple System Atrophy Rating Scale.

Tab. 2: ANOVA- mixed design 2x2 with main effect for variable between groups-Group,main effect for variable within groups-Time and interaction effect between 2 factors.

TEST		**MSA-M (N:12)**	**MSA-F (N:14)**	**Main Effect Factor: time p**	**Main Effect Factor: group p**	**Interaction of Factors p**
Motor Assessments						
UMSARS I	**T0**	19.90±7.11	20.66±5.63	**0.007**	0.439	0.240
	T1	21.81±5.91	25.11±5.6			
UMSARS II	**T0**	21.54±6.54	23.11±6.88	**0.044**	0.323	0.428
	T1	23.36±6.03	27.11±6.77			
UMSARS IV	**T0**	2.70±0.82	2.77±0.83	**0.027**	0.323	**0.027**
	T1	2.70±0.82	3.33±0.7			
Cognitive Assessments						
MOCA global score	**T0**	22.5±4.03	19.78±5.19	*0.073*	0.095	0.743
	T1	21.5±4.37	18.35±4.55			
MOCA-Visuospatial	**T0**	3.50±1.16	2.78±1.31	0.202	0.119	0.778
	T1	3.16±1.02	2.57±1.08			
MOCA-executive function	**T0**	2.25±1.21	1.5±1.6	**0.010**	0.225	0.551
	T1	1.58±1.31	1.07±1.32			
MOCA-Language	**T0**	4.58±1.16	4.00±0.78	0.247	0.141	0.757
	T1	4.75±1.05	4.28±0.99			
MOCA-Orientation	**T0**	5.75±0.62	5.57±0.64	0.418	0.778	0.418
	T1	5.50±0.67	5.57±0.51			
MOCA-Attention	**T0**	5.33±0.98	4.14±1.7	0.978	**0.023**	0.718
	T1	5.41±0.99	4.07±1.73			

MOCA-Memory	**T0**	1.54±1.69	1.71±1.48	0.135	0.811	0.861
	T1	1.09±1.22	1.14±1.16			
Memory domain						
15-RAWLT	**T0**	36.00±11.73	35.85±12.50	0.373	0.582	0.111
	T1	31.58±15.15	37.14±12.84			
Prose memory	**T0**	10.76±2.46	11.75±5.79	0.164	0.934	0.293
	T1	10.40±3.42	9.19±4.34			
Recall of Rey Osterrieth figure	**T0**	15.95±7.87	10.60±6.54	0.132	**0.013**	0.202
	T1	19.7±8.89	10.92±6.74			
Attention domain						
TMT-part A	**T0**	62.08±37.28	78.64±33.24	**0.015**	0.105	**0.009**
	T1	61.33±39.20	96.07±46.83			
Stroop test-error interference	**T0**	10.79±12.1	8.85±13.58	**0.016**	0.695	0.771
	T1	3.75±7.12	3.25±3.70			
Executive domain						
CDT	**T0**	9.36±1.50	7.23±2.97	0.149	**0.020**	0.725
	T1	8.36±1.91	6.61±2.39			
SVF	**T0**	34.45±12.20	29.78±11.97	0.610	0.213	0.484
	T1	34.72±13.39	28.07±8.55			
Copy of the Rey Osterrieth figure	**T0**	30.37±5.77	26.39±7.45	**0.001**	**0.042**	0.294
	T1	26.66±8.2	19.96±6.75			
Visuospatial domain						
Constructional apraxia test	**T0**	11.58±2.27	11.5±5.89	*0.052*	0.197	0.114
	T1	11.25±1.76	8.42±1.86			
BJLO	**T0**	21.91±4.77	15.78±6.11	**0.043**	**0.010**	0.914
	T1	19.91±5.6	13.57±7.66			
Language domain						
ENPA-non word repetition	**T0**	3.54±1.43	4.30±0.75	0.476	0.561	**0.028**
	T1	4.27±0.64	3.92±1.11			
ENPA-auditory comprehension of sentences	**T0**	13.50±0.97	13.00±1.83	0.667	0.355	0.943
	T1	13.60±0.96	13.07±1.38			
Behavioral Assessments						
BDI-II	**T0**	12.27±7.98	17.14±10.57	0.502	0.163	0.881
	T1	11.27±7.86	15.57±9.46			
AES	**T0**	33.27±6.24	38.50±10.15	0.758	*0.057*	0.677
	T1	33.09±6.00	39.71±9.42			
Functional autonomy						
ADL	**T0**	4.66±1.77	4.35±1.86	**0.027**	0.142	0.147
	T1	4.33±1.82	2.857±1.7			
IADL	**T0**	4.5±1.83	5.53±1.98	**0.002**	0.636	0.083
	T1	3.83±1.64	3.38±1.89			

Values are shown in mean± standard deviation

Statistically significant differences are indicated in bold

15-RAWLT: Rey'sauditory 15-word learning test; ADL: Based Activities of Daily Life; AES: Apathy Evaluation Scale; BDI-II: Beck Depression Inventory II; BJLO: Benton'sJudgment of Line Orientation; CDT: Clock Drawing test; ENPA: Neuropsychological Examination of Aphasia battery; F: females; IADL: Instrumental Activities of Daily Life; M: males; MCI: Mild Cognitive Impairment; MoCA: Montreal Cognitive Assessment battery; MSA: multiple system atrophy;

p= p-value; SVP: Semantic Verbal Fluency; t: T Test; T_0: base-line; T_1: follow up; TMT: Trial Making Test; UMSARS:Unified Multiple System Atrophy Rating Scale.

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3.**Language profile in MSA patients: an investigation by MSA-tailoredSAND battery**

Article being submitted

3.1 Abstract

Background: The language profile of multiple system atrophy (MSA) is poorly described and its definition may contribute to more comprehensively characterize the disorder and clarify the involvement of the basal ganglia in language abilities.

Objective: In the present study we sought to validate a Screening for Aphasia in NeuroDegeneration (SAND) battery version specifically tailored on MSA patients and to describe language impairment in relation to MSA cognitive status and disease phenotype.

Methods and results: Forty patients with a diagnosis of MSA, 22HC and 17 PD were enrolled in the present study. By excluding the tasks with poor acceptability, we showed that the MSA-tailored SAND Global Score (MSAgs-SAND) is an acceptable, consistent and reliable tool to screen language disturbances in MSA. As for the discriminatory power of the MSAgs-SAND, the optimal cut off of 2 demonstrated an adequate sensitivity and specificity profile in identifying language impairment compared to both PD and HC.MSA patients performed worse than PD patients in sub-scores of Picture description task assessing number of nouns/number of total words and number of words. We did not find major differences between MSA phenotypes. We showed that MSA patients with mild cognitive impairment-multiple domain presented worse language performances as compared to patients with normal cognition and mild cognitive impairment- single domain.

Conclusions: The MSAgs-SAND is a consistent and reliable tool to screen language disturbances in MSA. Language disturbances characterize MSA patients irrespective of disease phenotype, and parallels the decline of global cognitive functions.

3.2 Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset, neurodegenerative disorder characterized by various combinations of parkinsonism, cerebellar ataxia, autonomic failure and corticospinal impairment. Specifically, the parkinsonian variant (MSA-P) is characterized by prominent akinetic-rigid parkinsonism and the cerebellar variant (MSA-C) by progressive ataxia (Stankovic et al., 2014).Cognitive impairment is common in MSA and involves primarily processing speed and attention/executive functions (Koga et al., 2017;Santangelo et al., 2018). Spatial planning skills, sustained attention, abstract thinking and verbal fluency are more commonly impaired (Stankovic et al., 2014; Koga et al., 2017). Secondly, working memory, recognition and recall of previously learned information and visuo-spatial skills are also impaired (Koga et al., 2007; Stankovic et al., 2014; Hara et al., 2018). Santangelo et al. (2018) showed that in MSA patients executive and linguistic dysfunctions were more common than memory and visuo-spatial deficits, however the language domain has been poorly studied so far. Speech disorder is a common clinical manifestation occurring in 70–100% of patients with Parkinson's Disease (PD) and atypical parkinsonian syndromes (APS) (Ho Ak et al., 1998; Kluin et al., 1996) and tends to emerge at an early stage (Kim et al., 2010; Rusz et al., 2011), however, there are few studies describing the language profile of APS in conjunction with the characteristics of the speech (Catricalà et al., 2019 ; Picillo et al., 2019) and there are no studies describing language profile of MSA-patients. Specifically, the literature estimated that abnormalities of speech are common in patients with APS and PD, with heterogeneous features (Sachin et al., 2008) and a significant impact on the subject's life, involving an increased requirement of physical and cognitive resources during conversations and social interactions (Miller et al., 2006). Primarily, the poor performances on linguistic tasks might be the consequence of speech disorders, such as dysarthria, which is a common clinical feature of AP (Rusz et al., 2015) and is related to basal ganglia pathology. Speech dysfunction in Parkinsonism may include mono-pitch, reduced stress, monoloudness, imprecise consonants, inappropriate silences, short rushes and harsh breathless voice illustrating articulatory dysfunction (Saxena et al., 2014). Inefficiency in naming tests has been reported in MSA patients with dementia as opposed to MSA patients without dementia (Kim et al., 2013).

There are no data about language differences between MSA-P and MSA-C. Huh and colleagues (2015) found that speech impairment has been commonly reported early in the disease stages of MSA-P and this feature has important prognostic and therapeutic relevance as compared to early PD.

The aim of our study was to investigate the language domain by a brief, standardized, custom-made instrument for the assessment of language disorders in subjects with neurodegenerative disease (Catricalà et al., 2017) and determine a clinical cut-off between MSA, PD and healthy controls (HC). Furthermore, we aimed: 1)to compare language profiles among MSA and PD patients, and HC, 2) to evaluate the language changes within MSA group according to different levels of cognitive efficiency, 3) to compare the language profile between MSA-P and MSA-C patients.

3.3 Methods

Patients

Between November 2015 and April 2019, 41 consecutive patients with a diagnosis of MSA according to current criteria (Gilman et al., 2008) were enrolled at the Center for Neurodegenerative Diseases of the University of Salerno.

Additional inclusion criteria for the present study were: (a) Italian native speaker; (b) sufficiently intelligible speech such that the intended target could be determined for the majority of words; (c) intact or corrected auditory and visual functions; (d) disease duration less than 10 years; (e) ability to complete the Screening battery for Aphasia in NeuroDegeneration (SAND) battery upon clinical judgment. Additional exclusion criteria included: (a) Mini-mental State Examination (MMSE) $\leq$ 10 (Battista et al., 2018).

In addition, two groups of age- and education-matched healthy controls HC and PD patients were also enrolled for the present study. Exclusion criteria for enrollment of PD patients were diagnosis of dementia according with MDS criteria and H&Y

in on state>3. HC with a history of head injury, and other neurological, psychiatric or physical illness which may affect cognition, were excluded.

The project was approved by the local Ethics Committee and each subject was included upon signature of the informed consent form.

Clinical and cognitive evaluations

The severity of the disease was assessed by Unified Multiple System Atrophy Rating Scale (UMSARS). The severity of dysarthria was assessed by means of the dysarthria-subitem score of the UMSARS-II (Wenning et al., 2004).

Cognitive abilities were screened with the Montreal Cognitive Assessment (MoCA). Memory domain was investigated with the delayed recall scores of the Rey auditory verbal learning test (15-RAWLT), Recall of Rey Osterrieth figure and the prose memory test. Attention domain was explored through the Trail Making Test (TMT) and the short version of the Stroop Interference Test. Executive functions were assessed with the Clock design test (CDT), semantic verbal fluency test (SVF) and Copy of the Rey Osterrieth figure. Visuo-spatial functions were tested with the constructional apraxia test and Benton orientation line test (BJLO). Language domain was explored with two sub-tests from the Neuropsychological Examination of Aphasia battery (ENPA), the non-word repetition test and the hearing comprehension test of sentences (Picillo et al., 2019). Functional autonomy was evaluated with the Instrumental Activities of Daily Life (IADL) and with the Basic Activities of Daily Life (ADL), while depression and apathy with the Beck Depression Inventory II (BDI-II), using cut-off>12, and Apathy Evaluation Scale (AES), using cut-off>37, respectively (Santangelo et al., 2014).

We used the z-scores of the individual tests and a control group to classify MSA with normal cognition (MSA-NC), MSA with MCI-single domain (MSA-MCIsd), MSA with MCI-multiple domain (MSA-MCImd) and MSA with dementia (MSA-D) and used Litvan's criteria to define MCI test (Litvan et al., 2012; Auzou et al.,

2015; Fiorenzato et al., 2019). Furthermore, we divided MSA patients according to the MOCA median value.

Language testing

Language was evaluated with the SAND battery, originally created for Primary Progressive Aphasia (PPA) and later associated with a global score for the identification of a clinical cut-off constituted by 23 task-related scores that was computed according with a specific process (PPAgs-SAND). In brief, the PPAgs-SAND is obtained by assigning to the individual involved sub-tests a score of 1 or 0 respectively based on the placement of the correct score below or above the cut-off. The sum of the scores 0 and 1 is performed and higher scores indicating more severe impairment. However, PPAgs-SAND acceptability and consistency in MSA patients was suboptimal due to a high proportion of missing data in the writing task. Therefore, a MSA-tailored SAND Global Score (MSAgs-SAND) was created, reducing the impact of the writing subscores and expanding the relevance of the remaining tasks subscores. The MSAgs-SAND ranges from 0 to 27, with higher scores indicating greater impairment (see *Supplementary material:Table1*).We used also sub-tests of Neuropsychological Examination of Aphasia battery (ENPA), phonemic and category fluency, CaGi naming (Catricalà et al., 2017; Battista et al., 2018).

3.4 Statistical Analysis

After checking for normality distribution with the Kolmogoroy-Smirnov' test, differences in variables between groups were computed with χ^2 or the Kruskal-Wallis tests as appropriate. Pairwise comparisons were performed with Mann-Whitney's U test.

Acceptability and internal consistency were explored for the both the PPAgs-SAND and the MSAgs-SAND. Acceptability was considered appropriate for each Global Score if ≤15 % of the respondents totalized the lowest and highest possible

scores (floor and ceiling effect) and for each Global Score item if there were ≤5 % of missing values. Internal consistency was evaluated by means of Cronbach's alpha (Cronbach, 1995). A value ≥ 0.70 was considered as acceptable (SAC, 2002). Since the PPAgs-SAND did not qualify as an acceptable and consistent tool to explore language in MSA patients, subsequent analyses were performed only for the MSAgs-SAND. Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation for both Global Scores (standard, ≥ 0.40) (Nunnally et al., 1994).

Construct validity was explored with non-parametric Spearman's correlation between the MSAgs-SAND and other language testing as well as with cognitive and behavioral testing. Correlations were considered strong with coefficient > 0.70 and moderate with coefficient between 0.30 and 0.70. ROC analysis was performed for the MSAgs-SAND to identify the optimal cut-off score to detect language impairment in MSA-patients compared to both PD and HC. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and diagnostic accuracy in comparison to clinical diagnosis were assessed at the best threshold for classification. Significance threshold was set at $p \leq 0.05$.

We divided the patients with MSA according to the severity of dysarthria calculated with UMSARS Item 2 and we investigated the differences of groups in language tests by Kruskal-Wallis tests. We used Spearman's correlations to investigate the relationship between dysarthria, duration of disease and MSAgs-SAND.

We compared by Kruskal-Wallis' tests, sub-tests of SAND and MSAgs-SAND of MSA with HC and PD patients and pairwise comparisons were performed with Mann-Whitney's U test. In order to investigate the percentage of alteration in the nine sub-tasks and compare the type of errors within the single sub-tests we used the chi-square test.

We compared sub-tests of SAND and MSAgs-SAND of MSA divided in NC, MCI-sd, MCI-md by Kruskal-Wallis tests and pair wise comparisons were performed with Mann-Whitney's U test. Dividing by median score of MOCA test, we compared MSAgs-SAND and item 2 of UMSARS by Mann-Whitney's U test.

Furthermore, we compared sub-tests of SAND and MSAgs-SAND from MSA-P and MSA-C patients with those from PD patients by means of Mann-Whitney's U test.

Statistical analysis was performed with SPSS (Version 23).

3.5 Results

Forty-one MSA patients were considered for the present study, but one was excluded due to not intelligible speech. The final cohort, thus, included 40MSA and 17 PD patients as well as 22 HC matched for age and education. Demographics and clinical data of enrolled patients are reported in **Table1**.

Validation phase

All items of PPAgs-SAND presented a good acceptability but writing task presented 9.8% of missing data. Cronbach's alpha was 0.696 and, thus, it was considered suboptimal for internal consistency. Removing the items presenting poor acceptability, such as writing task and adding sub-items of whole sub-tests significantly improved Cronbach's alpha from 0.696 to 0.815. Therefore, we used the MSAgs-SAND for following analyses *(see Supplementary material:Table 1).*Neither ceiling nor floor effects were observed for the MSAgs-SAND (lowest possible score=0, 12.2%; highest possible score=18, 2.4%). Skewness of the MSAgs-SAND was 1.280. All the MSAgs-SAND items presented excellent acceptability as there were no missing data and 100% of data were computable. Cronbach's alpha was 0.815 indicating high-level internal consistency. By removing additional items, no further improvement of Cronbach's alpha was detected. Spearman's correlation confirmed convergent validity of the single macro-tasks included in the MSAgs-SAND, demonstrating significant moderate correlation with other language tests administered (*see Supplementary material: Table2*). As for the other cognitive tests, moderate correlation was demonstrated with measures of global cognition as the MMSE and the MoCA, but no correlation

was shown with memory test and apathy (*see Supplementary material: Table3*). ROC analysis was used to assess the discriminatory power of the MSAgs-SAND in identifying language impairment in MSA compared to both HC and PD.

As for the comparison with HC, the ROC analysis showed a 74.9% discriminatory power (95%CI 62.8% to 87.0%). The optimal cut-off was 2 showing 60% sensitivity, 77.3% specificity, 82.8% positive predictive value (PPV), 51.5% negative predictive value (NPV) and 66.12% diagnostic accuracy (*see Supplementary material: Figure1A*). The cut-off 1 showed 75% sensitivity, 59.1% specificity, 76.9% positive predictive value (PPV), 56.5% negative predictive value (NPV) and 69.35% diagnostic accuracy. As for the comparison with PD, the ROC analysis showed a 68.5% (95%CI 53.1% to 83.9%) discriminatory power. The optimal cut-off was 2 showing 60% sensitivity, 76.5% specificity, 85.7% positive predictive value (PPV), 44.8% negative predictive value (NPV) and 64.91% diagnostic accuracy (*see Supplementary material: Figure 1*).

Dividing MSA patients in 3 groups according to the severity of dysarthria, we didn't find significant differences among groups in MSAgs-SAND (p=0.831); there was no significant correlation between MSAgs-SAND and both dysarthria-sub item score of the UMSARS-II (p=0.555) and disease duration (p=0.140).

Language differences between MSA, PD and HC

Comparing SAND-scores between MSA, HC and PD patients, we found that MSA performed worse in total MSAgs-SAND (p=0.001), in naming, repetition of words/no-words, repetition of predictable and unpredictable sentences, reading of words, total number of syntactic structures in picture description and writing I.U. sub-tests as compared to HC (p<0.05)**(Table2)**. MSA performed worse in MSAgs-SAND, in number of nouns/number of total words and number words in Picture description task than PD (p=0.026); there was a trend towards a significant difference between MSA and PD also in sentence repetition sub-test (p=0.055)**(Table2)**. PD performed better in number of nouns/number of total words and number of repaired sequences/number of words in Picture description task than

HC ($p<0.005$) and there was a trend for non-predictable sentence repetition sub-test ($p=0.057$) **(Table2).**

Qualitative analysis of SAND in MSA-patients

Within MSA group, 37.5% of patients were impaired in reading task, 30% in sentence repetition task, 22.5% in words and no-words repetition, 25% in I.U. picture description, 15% in writing task, 12.5% in naming and sentence comprehension, 10% in word comprehension, and 5% in semantic association **(p=0.**004); post-hoc analysis showed significant differences between word/no words repetition and semantic association ($p=0.002$), between sentence repetition and word comprehension ($p=0.02$), semantic association ($p=0.003$), between reading and naming ($p=0.009$), sentence comprehension ($p=0.009$), word comprehension ($p=0.003$), semantic association ($p=0.0003$), between semantic association and picture description I.U. ($p=0.01$) and writing I.U. ($p=0.02$) **(Figure1A).**Specifically, in naming task, MSA patients showed more mistakes with no-living (37.5%) than living (2.5%) items ($chi^2= 15.3$; $p=0.000$), while in connected speech task produced fewer verbs than nouns on the total of words ($p=0.023$)**(Figure1B).**

Language differences in MSA-patients according to global cognitive state and phenotipes

MSA-MCIsd performed better than MSA-MCImd, with better performance in sentence repetition task ($p<0.05$), with a trend towards a significant difference in naming nott living ($p=0.071$). MSA-MCImd showed worse scores than MSA-NC in MSAgs-SAND, naming of living and no-living, sentence comprehension, no-living comprehension, predictable and unpredictable sentence repetition, reading of words and no-words, semantic association, total words in Picture description task ($p<0.05$). MSA-MCIsd tended to perform worse in MSAgs-SAND than MSA-NC ($p=0.055$). There was no significant difference in the MSAgs-SAND between

MCI-md patients with and without alteration of the linguistic domain, measured by ENPA (U=6.00, p=0.655) (**Table3**).

By comparing MSA-patients divided into two groups according to the median MOCA score, patients with lower MOCA performed worse in single no-living words comprehension, predictable and unpredictable sentences repetition, words and no-words reading, semantic association, Picture description I.U., I.U. writing, number words and total number of syntactic structures produced in Picture description task as compared to patients with higher MOCA score ($p<0.05$). Patients with a lower MOCA score performed better in number of nouns/number of total words on Picture description than patients with a higher MOCA score ($p<0.05$) (**Table4**).

By comparing sub-tests of SAND and MSAgs-SAND among MSA-P, MSA-C and PD groups, MSA-C performed better than MSA-P in the number of repaired sequences/number of words in Picture description (U=110.50, p=0.005). MSA-P patients performed worse in auditory sentence comprehension than PD patients ($p<0.05$) (*see Supplementary material: Table4).* MSA-C patients performed worse than PD patents in MSAgs-SAND, words and sentence repetition, unpredictable sentence repetition, number of words, number nouns/number total words, total number of syntactic structures, number of repaired sequences/number of words, number of phonological errors/number of words in picture description task ($p<0.05$).

3.6 Discussion

In this paper we evaluated one often neglected aspect of cognitive impairment in movement disorders, that is language impairment. Indeed, recognizing language disturbances and their relationship with motor impairment can be useful in developing rehabilitation strategies. Moreover, the observation of linguistic production deficits in patients with a movement disorder, rather than primary language dysfunction, could improve knowledge about relationships between language and action representation (Leisman et al, 2016).

Validation phase

We found that the MSAgs-SAND, composed by 27 features, is an acceptable, reliable and easily applicable tool to explore language profile in MSA patients. By removing sub-scores with high proportion of missing values and expanding sub-scores of the remaining tasks, we used the best combination of SAND tasks to screen language ability in MSA leading to a significant improvement in consistency and acceptability as compared to the original SAND Global Score and PSP-tailored SAND (Acquadro et al., 2004; Catricalà et al., 2017; Picillo et al., 2019).

As a matter of fact, differently from patients with PPA, MSA patients disclose peculiar clinical features possibly impacting performances on specific language tasks and, specifically, the writing task can be affected by both dystonia and bradykinesia. The combination of SAND tasks included in MSAgs-SAND overcame such limits showing high acceptability, since data were computable for 100% and the percentage of missing values was 0% for all items. The excellent acceptability by MSA patients is also supported by the absence of both ceiling and floor effects. Furthermore, the internal consistency of MSAgs-SAND is high and acceptable (Cronbach's alpha = 0.815), suggesting a coherent representation of all the language functions screened. As for convergent construct validity, each task of the MSAgs-SAND showed significant moderate correlation values with other corresponding language testing. Furthermore, the MSAgs-SAND showed moderate correlation with measures of global cognition as well as with cognitive tests exploring attention-executive and visuo-spatial domains. As for the discriminatory power of the MSAgs-SAND, the optimal cut off of 2 demonstrated an adequate sensitivity and specificity profile in identifying language impairment compared to both PD and HC. This is the first study showing a clear cut off for a language battery differentiating MSA from PD and HC. Therefore, our results suggest that objective speech assessment may provide an inexpensive and widely applicable screening instrument for differentiation of MSA and PD. However, dysarthria, measured by the UMSARS-II item 2 wasn't related with MSAgs-SAND,

suggesting that SAND battery is useful to investigate different aspects of language other than speech, even if we cannot exclude that UMSARS-II item is not an accurate measure of dysarthria in MSA.

Language differences between MSA, PD and HC

MSA performed worse in MSAgs-SAND, naming, repetition of words/no-words, repetition of sentences, reading of words, total number of syntactic structures in picture description and writing I.U. sub-tests as compared to HC. Our results on the naming test are in line with the literature reports of impaired naming as a frequent feature of many different neurological disorders (Spezzaro, 2010). The naming performance may depend on the integrity non-linguistic abilities, thussupporting the hypothesis that impairment language abilities in MSA can be interpreted within an embodied cognition framework (Antzoulatos and Miller, 2011). Our results on repetition task could be explained by the dysexecutive deficits commonly found in MSA, and specifically by altered interactions among working memory, processing speed and language domain (Archibald and Joanisse, 2009; Hesketh and Conti-Ramsden, 2013; Santangelo et al., 2018). Therefore, we suggest that language deficits in MSA are not only related to speech problems (Joanisse and Seidenberg, 1998; Leonard, 2014), but also to alterations executive function and embodiment.

MSA performed worse than PD patients in MSAgs-SAND in sub-scores of Picture description task, specifically in number of nouns/number of total words and number words than PD patients. The differences found between MSA and PD patients are consistent with a previous study, assessing MSA and PD patients by sub-tests of E.N.P.A. and showing no significant differences between groups (Santangelo et al., 2018). However, in the current study we used a more extensive language battery and included a greater number of patients than the previous one. Moreover, we investigated language more specifically with a tool that was created specifically for neurodegenerative diseases. In fact, EN.P.A. was born to investigate focal or diffuse aphasic deficits but the tests are very simple because they are suitable for severe aphasic patients and also with low schooling, it is possible that there are no significant differences due to the simplicity of the tests.

In Santangelo et al. (2018) there was a significant difference in the test of fluency, but this test also investigates the executive functions so it is not suitable for evaluating the language in patients who already have problems including disexecutive problems.

Qualitative analysis of SAND in MSA-patients

As for the nine sub-components of language assessed with SAND, our MSA patients showed higher percentage of impairment in reading (37.5%) and repetition tasks (30%) than other sub-tests. These results are in line with speech and executive deficits already described in MSA patients (Soliveri et al., 2000; Lange et al., 2003 Sachin et al., 2008).

Moreover, in naming task, MSA patients showed a worse performance on no-living than living items. No previous study has performed a qualitative analysis of language in MSA, while more evidence is available in PD patients (Ho et al., 1999). In PD, semantic deficits, both in production and comprehension, are much more severe when verbs or nouns have an action-related component (Bocanegra et al., 2015; Cardona et al., 2013; Humphries et al., 2016), suggesting that the lexical-semantic information processing of action words depends on the integrity of the motor system (Boulanger et al., 2008). Taken together, our and previous results suggest that the deficit in the processing of action-related language in both PD and MSA might depend on a dysfunction of embodiment resulting from basal ganglia dysfunction (Bocanegra et al., 2015; Cardona et al., 2013).Furthermore, deficits on no-living items may also involve a selective functional damage. In fact, Devlin et al. (1998) proposed that an initial damage to the cognitive network may be associated with a greater deficit for no-living than living, since isolated distinctive properties of no-living could be more easily damaged, while the densely inter-correlated properties of living may be able to compensate such damage. The greater impairment on verbs than nouns on picture description in our MSA patients is consistent with the major impairment observed in patients with PD, as compared to object naming (Cotelli et al., 2018).

Language differences in MSA-patients according to global cognitive state and phenotypes

As for the relationship between language and cognitive status, we detected worse language performance in MSA patients with MSA-MCImd, compared to MSA-NC in total MSAgs-SAND, naming, reading and semantic association. Moreover, patients that had lower scores at the MOCA test performed worse in MSAgs-SAND, naming, no-living words comprehension, sentence repetition, reading, semantic association, I.U. of picture description and writing, suggesting that language deficit may be related to the extent of impairment of the cognitive networks. This result was in line with the inefficiency in naming tests reported in 6 MSA patients with dementia as opposed to 9 MSA patients without dementia (Kim et al., 2013). Indeed, also in PD the global cognitive profile may influence naming performances (Bocanegra et al., 2015). We did not find differences between MSA-C and MSA-P phenotypes in MSAgs SAND. Therefore, we suggest that the language profile in MSA patients does not change according to the motor phenotype but according to the patients' cognitive impairment.

Conclusion

Our study contributes to clarify the role of the basal ganglia in language. The basal ganglia are crucial elements in language functions and it has been recognized that the language abilities may be altered in patients affected by basal ganglia pathology (Leisman et al., 2014). In this regard, Florenzano and colleagues (2019) studied language impairment by assessing phonemic fluency, semantic fluency and naming task in atypical parkinsonism and found that patients with PSP performed worse than MSA in fluency tasks, while there were no significant differences between MSA and PSP in naming task. Previous reports suggested a mild language impairment in MSA and, indeed, patients with MSA, PD and Lewy Body Disorder (DLB) performed equally well on simple tests of sentence repetition, object naming and lexical fluency (Kao et al., 2009). Specifically, both DLB and MSA subjects

showed decreased semantic fluency as compared to PD subjects (Kao et al., 2009). In this study, we first investigated the properties of a new language screening test in MSA patients and were able to comprehensively asses a cognitive domain that has been previously studied only by semantic, phonemic and naming tasks. By applying this new tool in MSA, our study provides new evidence supporting the notion of a language-movement relationship, that would depend on integration between cortical and sub-cortical areas (Cardona et al. 2013) and sustains the hypothesis that the key aspects of human language are supported by brain mechanisms originally developed for sensory motor integration (Gallese, 2008). Finally, given the strong link between language and hearing and knowing that the a-synuclein is mainly found in the efferent neuronal system inside the inner ear and this could influence the susceptibility to hearing loss, as already demonstrated in PD patients that showed impaired speech discrimination abilities compared with control group (Vitale et al., 2016), in the future it will also be important to better understand the relationship between the subdomains of the language studied with SAND and hearing in patients with MSA that may have audio-vestibular dysfunction even in the absence of self-reported auditory or vestibular symptoms (Scarpa et al., 2020).

Table 1. Demographic and clinical features of the enrolled cohort.

	MSA (N=40) median (IQR)	**PD (N=17)** median (IQR)	**HC (N=22)** median (IQR)	**P**
Age	62.0 (11.0)	64.0 (3.0)	64 (7.0)	.073
Education	11.0 (7.0)	10.0 (11.0)	8.0 (7.8)	.736
Disease duration (Years)	4.00 (4.0)	6.00 (6.0)	NA	.357
MMSE	27.0 (5.0)	28.0 (3.0)	27.5 (2.3)	.688
UMSARS-I	22.5 (11.5)	NA	NA	NA
UMSARS-II	25.0 (10.5)	NA	NA	NA
UMSARS-IV	3.00 (2.0)	NA	NA	NA
UPDRS	NA	18 (16.0)	NA	NA

Data are in median (Interquartile range=IQR), unless otherwise specified.

Abbreviations: a: MSA versus HC $p<0.05$; b: MSA versus PD $p<0.05$; HC: healthy controls; MMSE: Mini-mental State Examination; MSA= multiple system atrophy;NA: not applicable; PD: Parkinson's disease; SAND: Screening for Aphasia in NeuroDegeneration; UMSARS: Unified Multiple System Atrophy Rating Scale;UPDRS= UnifiedParkinson'sDisease Rating Scale.

Table 2: Comparisons of MSAgs-SAND and SAND sub-test scores among MSA, PD and HC

	MSA (N=40) median (IQR)	**PD (N=17) median (IQR)**	**HC (N=22) median (IQR)**	**Test Kruskal Wallis**	**P**
MSAgs-SAND	4 (5.5)	1 (2.0)	1 (3.0)	12.20	**.002**[a,b]
Picture Naming total	12.00 (2.28)	13.00 (2.0)	13.00 (2.0)	6.59	**.037**[a]
Picture Naming- living	6.50 (1.50)	7.00 (1.75)	7.00 (1.0)	3.70	.157
Picture Naming- no-living	6.00 (2.0)	7.00 (1.0)	7.00 (1.50)	4.76	.920
Auditory Sentence comprehension	8.00 (1.0)	8.00 (0.00)	8.00 (0.50)	3.32	.190
Single Word comprehension-total	12.00 (1.0)	12.00 (0.50)	12.00 (2.0)	1.63	.441
Single Word comprehension-living	6.00 (0.0)	6.00 (0.0)	6.00 (0.0)	0.938	.626
Single Word comprehension-no-living	6.00 (1.0)	6.00 (0.0)	6.00 (1.0)	0.799	.671
Words/no-words repetition-total	7.00 (1.50)	9.00 (1.50)	9.00 (2.0)	13.35	**.001**[a]
Words repetition	6.00 (1.0)	6.00 (0.0)	6.00 (1.0)	7.95	**.019**[a]
No-words repetition	2.00 (2.0)	3.00 (1.50)	3.00 (2.0)	6.68	**.035**[a]
Sentence repetition-total	3.00 (2.50)	4.00 (2.50)	5.00 (1.50)	13.59	**.001**[a,d]
Predictable Sentence repetition	2.00 (1.50)	2.00 (2.0)	3.00(1.0)	10.91	**.004**[a]
Unpredictable Sentence repetition	2.00 (1.00)	2.00 (2.0)	2.00 (1.00)	10.26	**.006**[a,e]
Reading-total	14.00 (4.0)	15.00 (1.50)	16.00 (1.0)	9.80	**.007**[a]
Words reading	11.00 (2.0)	12.00 (1.0)	12.00 (0.50)	7.19	**.027**[a]
No-words reading	4.00 (1.0)	4.00 (1.0)	4.00 (1.0)	2.00	.368
Writing I.U.	3.00 (2.50)	4.00 (4.0)	5.00 (1.00)	13.25	**.001**[a]
Semantic association	3.00 (1.0)	4.00 (1.0)	4.00 (1.0)	1.24	.537
Picture description I.U.	5.00 (3.50)	6.00 (4.0)	5.00 (3.0)	0.109	.094
Number words- Picture description	61.00 (55.0)	91.00 (68.00)	83.00 (62.0)	7.561	**.023**[b]
Number of nouns/number of total words- Picture description	0.29 (0.11)	0.25 (0.07)	0.29 (0.06)	8.202	**.017**[b,c]
Number of verbs/number of total words- Picture description	0.15 (0.08)	0.14 (0.07)	0.17 (0.06)	1.865	.394
Total number of syntactic structures- Picture description	8.00 (6.50)	10.00 (8.00)	10.00 (6.50)	7.695	**.021**[a,d]
Number of subordinates/total number of syntactic structures- Picture description	0.16 (0.52)	0.30(0.24)	0.20 (0.63)	1.157	.561
Number of repaired sequences/number of words- Picture description	0.00 (0.01)	0.01 (0.05)	0.00 (0.00)	10.886	**.004**[c,e]
Number of phonological errors/number of words- Picture description	0.00 (0.01)	0.00 (0.0)	0.00 (0.0)	13.478	**.001**[a,c]
Lexical-semantic errors/number of words- Picture description	0.00 (0.01)	0.00 (0.00)	0.00 (0.00)	8.219	**.016**[a]

Data are in median (Interquartile range=IQR), unless otherwise specified.

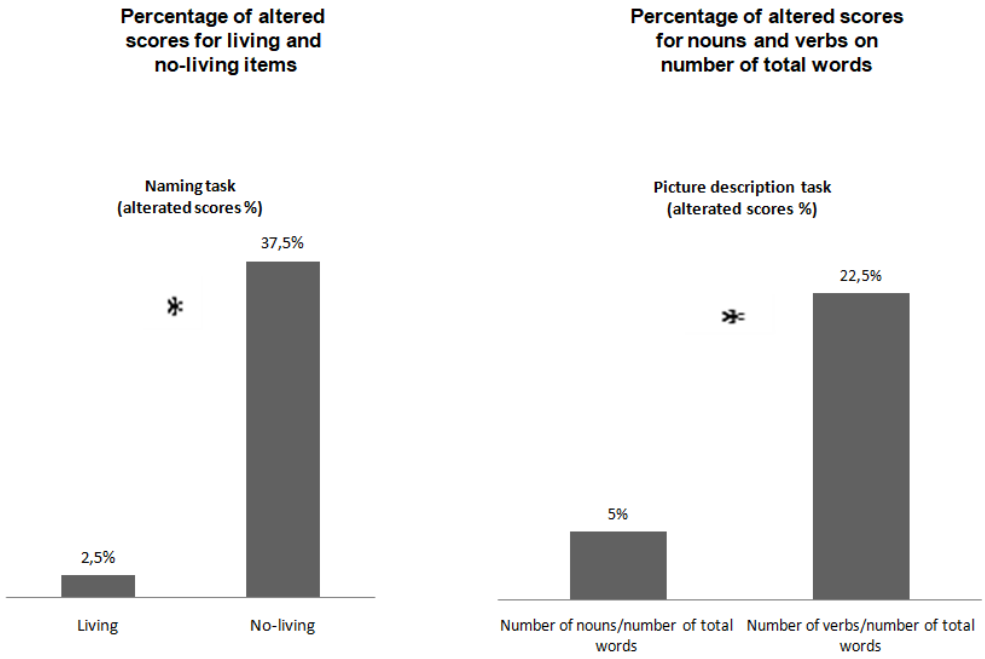
Abbreviations: a: MSA versus HC p<0.05;b: MSA versus PD p<0.05;c: PD vs HC p<0.05 d: MSA vs PD p=0.055; e: MSA vs PD p=0.057. HC: healthy controls; I.U.: information units; MSA: multiple system atrophy; PD: Parkinson's disease; SAND= Screening for Aphasia in NeuroDegeneration; MSAgs-SAND: MSA-tailored SAND Global Score.

Figure1:A)Percentage of altered scores in each subtests of SAND, in MSA patients; B)Percentage of altered scores for living and no living items in naming task and for nouns and verbs on total of words in picture description task.

A)

Statistically significant differences:
** word/no words repatition vs semantic association p=0.002;*
+ sentence repetition vs word comprehension p=0.02;
° sentence repetition vs semantic association p=0.003;
 # reading vs naming P=0.009;
§ reading vs sentence comprehension p=0.009;
ç reading vs word comprehension p=0.003;
¤ reading vs semantic association p=0.0003;
¥ semantic association vs picture description I.U. p=0.01;
∫ semantic association vs writing I.U p=0.02
Abbreviations: I.U.: information units; MSA: multiple system atrophy; SAND= Screening for Aphasia in NeuroDegeneration.

B)



* Significant differences (p<0.05)

Table 3.: Comparisons of MSAgs-SAND and SAND sub-testscores among MSA-NC, MSA-MCI-sd and MSA-MCI-md.

TEST	NC (N=25)	MCI-sd (N=6)	MCI-md (N=8)	Kruskal-Wallis'TEST	P
Clinical variables					
Age	60.50(9.3)	62.50(15.0)	66.0(11.0)	8.979	.011
Education	10.00(7.3)	10.50(8.8)	6.00(3.0)	6.91	.030
UMSARS I	19.50(12.5)	20.00(22.0)	28.0(7.0)	4.77	.090
UMSARS II	24.50(11.3)	25.00(17.8)	28.0(19.0)	2.670	.263
UMSARS III	2.50(1.3)	2.00(1.5)	3.00(1.0)	3.910	.142
Language assessment					
MSAgs-SAND	2 (3.5)	5 (6)	9.5 (8.5)	12.168	**.002**[c.d]
Picture Naming- Total	13.00(1.63)	11.00(3.50)	9.50(4.0)	9.708	**.008**[c]
Picture Naming- living	7.00(1.00)	5.00(1.50)	5.00(2.50)	13.043	**.001**[b. c]
Picture Naming- no-living	6.03(2.0)	6.00(2.0)	5.00(2.0)	6.555	**.038**[c]
Auditory Sentence comprehension	8.00(1.0)	7.00(1.50)	7.00(4.0)	4.985	.083
Single Word comprehension- Total	12.00(0.25)	11.50(1.0)	11.00(4.0)	11.095	**.004**[b]
Single Word comprehension- living	6.00(0.0)	6.00 (0.5)	6.00(1.5)	.199	.905
Single Word comprehension- no-living	6.00(0.0)	5.50(1.0)	5.00(1.0)	9.409	**.009**[c]

Words/no-words repetition- Total	8.00(2.0)	7.00 (1.5)	6.50(2.0)	8.647	**.013**
Words repetition	6.00(0.25)	6.00(0.75)	6.00(1.00)	2.293	.318
No-words repetition	2.00 (2.00)	1.00 (2.30)	1.00 (2.80)	4.892	.087
Sentence repetition- Total	3.00(2.00)	3.00(0.75)	2.00(1.00)	10.961	**.004**[a. c]
Predictable Sentence repetition	2.00(2.0)	1.50(1.75)	1.00(0.0)	7.494	**.024**[c]
Unpredictable Sentence repetition	2.00(1.25)	1.50(1.0)	1.00(1.0)	7.302	**.026**[c]
Reading- Total	15.00(3.25)	14.00(2.75)	12.00(6.0)	5.462	.065
Words reading	11.50(2.0)	10.50(2.50)	10.00(4.0)	6.291	**.043**[c]
No-words reading	4.00(0.0)	3.00(0.75)	3.00(2.0)	14.804	**.001**[b. c]
Writing I.U.	3.50(2.0)	2.50(2.50)	3.00(4.0)	4.489	.106
Semantic associations	4.00(1.0)	3.00(2.25)	2.00(2.0)	12.701	**.002**[c]
Picture description I.U.	5.00(4.00)	5.50(4.0)	5.00(5.00)	1.960	.375
Number words	64.5(59.5)	57.5(131.75)	38.0(34.0)	6.483	**.039**[c]
Number of nouns/number of total words	0.28(0.11)	0.38(0.28)	0.30(0.06)	3.716	.156
Number of verbs/number of total words	0.15(0.07)	0.17(0.17)	0.11(0.07)	1.932	.381
Total number of syntactic structures	8.00(5.50)	7.00(13.25)	4.00(7.0)	5.415	.067

Data are in median (Interquartile range=IQR), unless otherwise specified.

Abbreviations: a:MSA-MCIsd versus MSA-MCImd p<0.05; b MSA-MCIsd vs MSA-NC p<0.05; c: MSA-MCImd vs MSA-NC p<0.05; d: MSA-MCIsd vs MSA-NC p=0.055. I.U.: information units; MCI-md: mild cognitive impairment- multiple domain; MCI-sd: mild cognitive impairment- single domain; MSA: multiple system atrophy; NC= normal cognition; SAND= Screening for Aphasia in NeuroDegeneration; MSAgs-SAND: MSA-tailored SAND Global Score.

Table 4: Comparisons of MSAgs-SAND and SAND sub-test scores between MSA patients with MOCA higher and lower than the median score.

	MSA with Moca≥ median (N=22) median (IQR)	**MSA with Moca ≤ median (N=18)** median (IQR)	**U**	**P**
Clinical variables				
Age	60.00 (6.0)	64.00 (13.25)	84.500	**.004**
Education	13.00 (8.0)	5.00 (3.0)	55.500	**.000**
Duration	5.00 (3.00)	4.00 (4.25)	126.000	.558
UMSARS I	19.00 (13.0)	23.50 (8.25)	122.500	.163
UMSARS II	24.00 (11.0)	26.00 (10.75)	102.50	**.044**
UMSARS IV	2.00 (1.0)	3.00 (1.75)	112.000	.106
Language assessment				
MSAgs-SAND	2.5 (4.0)	6.00 (8.0)	111.500	**.018**

Picture Naming- Total	13.00 (1.50)	10.50 (2.41)	127.500	*.053*
Picture Naming- living	7.00 (1.00)	6.00 (1.88)	132.000	.062
Picture Naming- no-living	6.50 (3.00)	5.00 (1.88)	137.500	.088
Auditory Sentence comprehension	8.00 (1.00)	7.00 (1.00)	178.000	.527
Single Word comprehension-Total	12.00 (0.00)	11.00 (1.00)	74.500	**.000**
Single Word comprehension-living	6.00 (0.0)	6.00 (0.75)	161.000	.128
Single Word comprehension- no-living	6.00 (0.0)	5.00 (1.00)	102.000	**.002**
Words/no-words repetition-Total	8.00 (2.0)	7.50 (2.50)	178.000	.574
Words repetition	6.00 (0.0)	6.00 (1.0)	161.000	.209
Nonwords repetition	2.00 (2.0)	1.50 (1.75)	175.500	.529
Sentence repetition- Total	4.00 (2.0)	2.00 (1.00)	78.000	**.001**
Predictable Sentence repetition	2.00 (2.0)	1.00 (0.0)	97.000	**.003**
Unpredictable Sentence repetition	2.00 (2.0)	1.00 (0.75)	109.000	**.010**
Reading- Total	15.00 (2.0)	12.50 (5.25)	93.500	**.004**
Words reading	12.00 (2.00)	10.00 (3.75)	108.000	**.010**
No-words reading	4.00 (1.0)	3 (1.75)	127.000	**.025**
Writing I.U.	5.00 (1.0)	3.00 (1.0)	93.000	**.018**
Semantic association	4.0 (1.0)	3.00 (1.0)	113.000	**.013**
Picture description I.U.	7.00 (3.0)	4.00 (3.75)	124.000	**.041**
Number words	89.00 (74.0)	39.00 (20.0)	91.500	**.004**
Number of nouns/number of total words	0.28 (0.11)	0.31 (0.09)	96.000	**.005**
Number of verbs/number of total words	0.14 (0.08)	0.14 (0.12)	180.500	.634
Total number of syntactic structures	11.00 (7.00)	6.00 (4.25)	84.000	**.002**
Number of subordinates/total number of syntactic structures	0.29 (0.45)	0.00 (0.16)	144.000	.133
Number of repaired sequences/number of words	0.00 (0.02)	0.00 (0.0)	147.000	.110
Number of phonological errors/number of words	0.00 (0.01)	0.00 (0.02)	173.500	.459
Lexical-semantic errors/number of words	0.01 (0.01)	0.00 (0.03)	180.500	.607

Data are in median (Interquartile range=IQR), unless otherwise specified.

Abbreviations: I.U.: information units; MOCA: Montreal Cognitive Assessment battery; MSA: multiple system atrophy; SAND= Screening for Aphasia in NeuroDegeneration; MSAgs-SAND: MSA-tailored SAND Global Score.

Supplementary material- Table 1

SAND Global score (0-23) **(Battista et al., 2018)**	**MSA-tailored SAND Global score (Our proposal)**
A)Naming	**A**)Naming
1)Total	1)Total
B)Sentence comprehension	2)Living
C)Single word comprehension	3)Not-living
1)Total	**B**)Sentence comprehension
D)Repetition	**C**)Single word comprehension
1)Total	1)Total
E)Sentence repetition	2)Living
1)Total	3)Non-living
F)Reading	**D**)Repetition
1)Total	1)Total
G)Semantic associations	2)Words
H)Writing	3)No-words
1)Information units	**E**)Sentence repetition
2)Total words	1)Total
3)Nouns/total words	2)Predictable
4)Verbs/total words	3)Unpredictable
5)sentences	**F**)Reading
6)Orthographic errors	1)Total
7)semantic errors	2)Words (regular and irregular)
I)Picture description	3)No-words
1)Informative units	**G**) Writing
2)Number of words	1)Information units
3)Nouns/words	**H**)Semantic associations
4)Verbs/words	**I**)Picture description

5)Repaired sequences/number of words 6)Sentences 7)Subordinate/sentences 8)Phonological errors/number of words 9)Semantic errors/number of words	1)Informative units 2)Number of words 3)Nouns/words 4)Verbs/words 5)Repaired sequences/number of words 6)Sentences 7)Subordinate/sentences 8)Phonological errors/number of words 9)Semantic errors/number of words

SAND Global score acceptability and consistency in MSA patients was suboptimal due to a high proportion of missing data in the writing tasks. Therefore, following the three steps process as noted above, a MSA-tailored SAND Global Score was created, reducing the impact of the writing subscores and expanding the relevance of the remaining tasks subscores. The MSA-tailored SAND Global Score ranges from 0 to 27, with higher scores indicating greater impairment.

By reducing the items of writing tasks and expanding the items of other tasks, acceptability of the SAND battery presented a significant improvement (see Results).

Additional inclusion criteria for the present study were: (a) Italian native speaker status; (b) sufficiently intelligible speech such that the intended target could be determined for the majority of words; (c) intact or corrected auditory and visual functions; (d) disease duration less than 10 years; (e) successful completion of the language testing. Additional exclusion criteria included: (a) Mini-Mental State Examination (MMSE) < 10 (Battista et al., 2018).

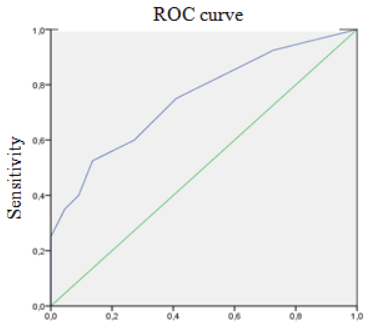
Supplementary Figure1: a) Summary of the diagnostic accuracy of the SAND battery for the comparison of MSA patients versus HC. **b)**ROC curve for the Global Score of the SAND battery to detect patients with language dysfunction evacuate in the sample of MSA patients versus HC. **c)**Summary of the diagnostic accuracy of the SAND battery for the comparison of PD patients versus MSA patients. **d)**ROC curve for the Global Score of the SAND battery to detect patients with language dysfunction evaluated in the comparison of MSA patients versus PD patients.La metterei nel testo principale, solo la ROC MSA vs PD

a)

MSA vs HC

	+	-	
Global Score MSA ≤ 2(-) SAND Global Score MSA >2 (+)	16	17	PPV 82.8%
	24	5	NPV 51.5%
	Sensitivity 60%	Specificity 77.3%	

b)

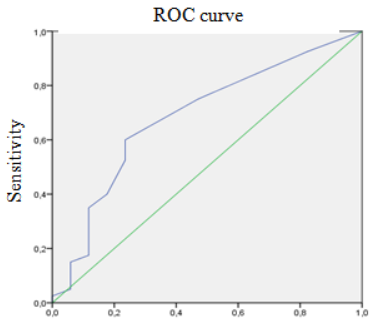


c)

MSA vs PD

	MSA +	- PD	
Global Score MSA ≤ 2(-) SAND Global Score MSA >2 (+)	16	13	PPV 85.7%
	24	4	NPV 44.8%
	Sensitivity 60%	Specificity 76.5%	

d)



Abbreviations: HC: healthy controls; MSA: multiple system atrophy; NPV: negative predictive value; PD: Parkinson's disease; PPV: positive predictive value; ROC: receiver operating characteristic; SAND: Screening for Aphasia in NeuroDegeneration.

Supplementary Table 2.: Spearman's correlation between single tasks of the MSA-tailored Global Score and other language tests.

SAND Task	**Language tests**	**Spearman's correlation**	**P**
Naming	*Phonemic fluency* *Category fluency* *CaGi naming*	0.470 0.474 0.611	**.002** **.002** **.002**
Word comprehension	*Phonemic fluency* *Category fluency* *Auditory sentence comprehension (ENPA)*	0.528 0.682 0.646	**.000** **.000** **.004**
Sentence comprehension	*Phonemic fluency* *Auditory sentence comprehension (ENPA)*	0.447 0.280	**.004** **.085**
Words/no-words repetition	*Phonemic fluency* *Category fluency*	0.315 0.330	**.047** **.038**
Sentence repetition	*Sentence repetition (ENPA)* *Buccofacial apraxia test*	0.500 0.395	**.001** **.046**
Reading	*Word repetition (ENPA)* *Sentence repetition (ENPA)* *Auditory sentence comprehension*	0.443 0.419 0.507	**.005** **.009** **.032**

	(ENPA) *CaGi naming*	0.467	**.025**
Writing I.U.	*Phonemic fluency* *Category fluency* *No-word repetition (ENPA)* *Sentence repetition (ENPA)* *Auditory sentence comprehension (ENPA)*	0.474 0.367 0.459 0.519 0.436	**.003** **.027** **.005** **.001** **.009**
Semantic association	*Phonemic fluency* *Category fluency* *Auditory sentence comprehension (ENPA)* *CaGi naming*	0.446 0.455 0.444 0.443	**.004** **.003** **.005** **.034**
Picture description I.U.	*Phonemic fluency* *Sentence repetition (ENPA)* *Auditory sentence comprehension (ENPA)*	**0.493** **0.430** **0.477**	**.001** **.006** **.002**

Significant differences are highlighted in bold.

Abbreviations: ENPA: Neuropsychological Examination of Aphasia battery, I.U.: information units; SAND= Screening for Aphasia in NeuroDegeneratio

Supplementary Table 3. Spearman's correlation between the MSA-tailored Global Score MSA and non-language tests.

	Spearman's correlation	**P**
Screening of global cognition		
MMSE	-.544**	**.001**
MoCA	-.507**	**.001**
Memory		
RAVLT immediate	-.288	.072
Prosa test	-.042	.796
Visuo-spatial functioning		
Constructional apraxia	-.536**	**.000**
BJLO	-.640	**.000**
Attention-executive functions		
CDT	-.368*	**.023**
TMT-A	0.618**	**.000**
Behavioral tests		
BDI-II	.335	**.049**
AES	.259	.111

Significance threshold corrected for multiple comparisons < 0.001

Abbreviations: AES: Apathy Evaluation Scale; BDI-II: Beck Depression Inventory II; BJLO: Benton's Judgment of Line Orientation; CDT: Clock Drawing test; MMSE: Mini-Mental State Examinaton; MoCA: Montreal Cognitive Assessment battery; PSP-rs: Progressive Supranuclear Palsy – rating scale; RAVLT: Rey's auditory 15-word learning test; RCF: Rey figure test; TMT-A: Trial Making Test.

*Supplementary Table 4:*Comparisons of MSAgs-SAND and SAND sub-test scores of SAND between MSA-P and PD patients.

	MSA-P **N= 20** **median (IQR)**	**PD** **N= 17** **median (IQR)**	**U**	**P**
Age	62.00(11.5)	64 (3)	122	.149
Education	8.00(6.0)	10 (11)	152	.578
Duration	5.0 (5.0)	6 (6)	82	.585
MSAgs-SAND	3.5 (5.8)	1 (2)	116.5	.098
Picture Naming total	13.00(1.50)	13.00 (2.0)	124	.152
Picture Naming- living	6.50(1.0)	7.00 (1.75)	154.5	.614
Picture Naming- no-living	6.00(2.0)	7.00 (1.0)	125.5	.145
Auditory Sentence comprehension	7.00(1.0)	8.00 (0.00)	112	**.033**
Single Word comprehension	12.00(1.0)	12.00 (0.50)	140	.269
Single Word comprehension- living	6.00(0.50)	6.00 (0.0)	156.5	.567
Single Word comprehension- no-living	6.00(0.48)	6.00 (0.0)	165	.839
Words/nonwords repetition	7.00(1.50)	9.00 (1.50)	118	.104
Words repetition	6.00(0.0)	6.00 (0.0)	147.5	.248
Nonwords repetition	2.00(2.0)	3.00 (1.50)	149	.507
Sentence repetition	4.00(2.5)	4.00 (2.50)	128	.193
Predictable Sentence repetition	2.00(1.50)	2.00 (2.0)	134	.246
Unpredictable Sentence repetition	2.00(2.0)	2.00 (2.0)	139	.323
Reading	15.00(3.50)	15.00 (1.50)	123.5	.142
Words reading	12.00(2.50)	12.00 (1.0)	137.5	.279
Nonwords reading	4.00(1.0)	4.00 (1.0)	148.5	.457
Writing I.U.	3.00(2.0)	4.00 (4.0)	134	.713
Semantic association	3.00 (1.8)	4.00 (1.0)	140	.322
Picture description I.U.	6.00(5.50)	6.00 (4.0)	155.5	.654
Number words	84.00(77.50)	91.00 (68.00)	109.000	.063
Number of nouns/number of total words	0.28(0.09)	0.25 (0.07)	133.500	.265
Number of verbs/number of total words	0.14(0.09)	0.14 (0.07)	167.500	.939
Total number of syntactic structures	8.00(8.0)	10.00 (8.00)	121.500	.138
Number of subordinates/total number of syntactic structures	0.17(0.52)	0.30(0.24)	140.000	.357
Number of repaired sequences/number of words	0.01(0.02)	0.01 (0.05)	146.500	.461
Number of phonological errors/number of words	0.00(0.01)	0.00 (0.0)	145.500	.340
Lexico-semantic errors/number of words	0.00(0.01)	0.00 (0.00)	139.000	.268

Significant differences are highlighted in bold.

Abbreviations: I.U.: information units, MSA-P: multiple system atrophy with predominantly parkinsonism, PD Parkinson Disease. SAND= Screening for Aphasia in NeuroDegeneration; MSAgs-SAND: MSA-tailored SAND Global Score.

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Chapter V

CONCLUSION

1. Conclusion

From November 2016 to September 2019, at the University Hospital of Salerno and in collaboration, where necessary, with other Italian centers, data collection and processing work was carried out on a sample of healthy subjects (HC) and patients with movement disorders, divided into patients with Parkinson's disease (PD), Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP) and CorticoBasal Syndrome (CBS).

The macroscopic objective of the present work was to investigate the cognitive and behavioral aspects in patients with rare parkinsonian syndromes and to investigate aspects poorly studied so far, such as language, quality of life and gender role.

In order to understand the value of neuropsychology as a biomarker in atypical parkinsonisms, we used a very extensive neuropsychological battery.

We applied the concept of mildcognitive decline with single-domain and multiple-domain involvement in atypical parkinsonian syndromes.

First of all, in order to widen the tools for the analysis of language in neurodegenerative diseases and to be able to use a more complete instrument, we implemented a screening battery, composed of nine tests (picture naming, word and sentence comprehension, word and sentence repetition, reading, semantic association, writing and picture description).

It’s useful to apply a short battery to investigate the components of language, because language is a very adaptive function and, if well analyzed, it may be able to convey more extensive cognitive information. The language in AP is usually conditioned by speech disorders, therefore a new reading of this domain was necessary with adequately constructed material.

Subsequently, comparing the neuropsychological and behavioral profile of MSA, PSP and PD patients, we found pervasive cognitive deficits, apathy and depressive symptoms in PSP, whereas little cognitive differences were found between PD and MSA. The findings indirectly supported a dysfunction of prefronto-subcortical circuitries (i.e., dorsolateral prefrontal and limbic circuits) in PSP and PD. Cognitive similarities between MSA and PD reinforced the pivotal role of altered basal ganglia and subsequent frontal deafferentation in the occurrence of the cognitive deficits.

We decided to study the disorders grouping them according to their clinicopathological characteristics, therefore we separately workedwith synucleinopathies and tauopathies.

Analyzing the PSP sample, we found that half of the cohort presented Richardson’s syndrome, followed by PSP with parkinsonism and corticobasal syndrome and that the only cognitive testing differentiating the phenotypes PSP-RS and PSP-CBS were semantic fluency and ideomotor apraxia. The majority of our cohort was either affected by dementia or presented normal cognition. Richardson’s syndrome presented the highest rate of dementia. The only marker of PSP non-Richardson’s syndrome phenotype was a better performance in visuo-spatial testing. In PSP, mild cognitive impairment likely represents an intermediate step from normal cognition to dementia.We analyzed the language profile of several phenotypes of PSP with SAND battery andshowed that the PSP-tailored SAND Global Score is an acceptable, consistent and reliable tool to screen language disturbances in PSP. We showed that language disturbances feature PSP patients irrespective of disease phenotype, but parallels the deterioration of the global cognitive function.

We applied CBS and PSP clinical diagnostic criteria to patients presenting with corticobasal syndrome and we found that PSP-CBS showed more severe clinical features compared to CBS according to the total PSP rating scale and subscores. We showed that both PSP and CBS criteria can be applied to such patients and that PSP-CBS showing a more severe form of disease in term of motor and cognitive impairment than CBS.

Assuming that promoting and maintaining an adequate quality of lifeis fundamental in neurodegenerative diseases both for the patient and his family, we worked on the translation, analysis of the psychometric propertiesand use of Parkinsonism Carers QoL (PQoLCarer) and PSP- QoL. We found that the scales are valid for the PSP sample and gender and geographic location presented a significant impact on the PSP-QoL in our sample with women and patients from the South of Italy scoring higher than their counterparts.

Analyzing the MSA sample data we found that at baseline assessment no patient with MSA was affected by dementia, whereas 66% of the whole MSA sample had a diagnosis of MCI. Specifically, MCI occurred in 61.9% of patients belonging to MSA-C group and in 68.9% of patients belonging to MSA-P but the comparison between MSA-P and MSA-C revealed no significant difference on any cognitive tests and apathy scale; instead, patients with MSA-P group had more reduced functional autonomy and more severe depression than patients with MSA-C. At follow-up evaluation, we found a significant worsening in cognitive tests assessing spatial planning and psychomotor speed in MSA-C group and a significant worsening in prose memory, spatial planning, repetition abilities and functional autonomy in MSA-P group.

Comparing MSA patients by gender we found that *c*ognitive and behavioural differences in MSA involve global cognition, planning, attention, visual-perceptive skills and depression, with female patients more compromised than males. Female patients deteriorated more than men over time as for motor functions and attention.

Finally, by analyzing the language profile in MSA patients we found that the MSA tailored SAND Global Score better represents language abilities in

MSA and that language disturbances feature MSA patients irrespective of disease phenotype, but parallels the deterioration of the global cognitive function.We partially contributed to better understand the role of the basal ganglia in language, thanks toour preliminary and exploratory findings.

In conclusion, it is important to study the cognitive-behavioral profile of patients with AP in greater detail, because at the moment there are still few studies assessing those issues and there is a high overlap of phenotypes. Cognitive and behavioral characterization of patients can improve knowledge about the different AP phenotypes and help to develop more specific treatment, both pharmacological and rehabilitative. Furthermore, it will be important to follow these patients over time, net of the generally rapid progression of these disorders, to identify strong prognostic predictors. Among the strengths of this work we include the presence of a fair number of patients with rare pathologies, the use of extensive cognitive battery for any studied pathology and the assessment of poorly investigated aspects that indeed have a great impact on patients' lives, such as language and quality of life. One major limitation is a limited presence of follow-up data, whereasthe exploratory nature of some data can be considered a limit.

The future objectives will be to expand the sample, also adding patients with DLB and frontal temporal dementia (FTD) to contribute to the debate between diversifications and overlaps with other diagnoses, to follow patients over time, to analyze the relationships between the quality of life of patients and their families, to validate behavioral scales in patients with AP, to understand the relationships between language and theory of mind and between cognitive and behavioral data and instrumental tests, such asOptical coherence tomography(OCT) and MRI.

Ringraziamenti

Al *Prof. Barone,* per avermi concesso il grande onore di lavorare nel suo gruppo di ricerca e per le preziose opportunità di apprendimento.

Alla *Prof.ssa Pellecchia,* costante ed affidabile punto di riferimento,esempio di competenza e profonda capacità di rispetto dell'altro.

Alla *Prof.ssa Santangelo,* che per prima ha creduto nelle mie capacità, permettendomi di mettermi in gioco in diversi contesti ed ampliando così le mie competenze.

Al *Prof. Vitale,* per aver accetatto di revisionare il mio lavoro di tesi e per i suggerimenti forniti.

Ad *Arianna,* per la vicinanza costante e la collaborazione fatta di rispetto e condivisione.

Ad *Imma e Maria,*per l'affidabilità dimostrata ed il contributo cruciale nei diversi lavori.

A *Susan*, per le fondamentali correzioni e per l'armonia che riesce ad elicitare ogni giorno con i suoi modi gentili.

Al *Dott. Erro,* per la fiducia riposta in me e le occasioni di crescita e miglioramento fornitemi costantemente ed in modo eterogeneo in questi anni.

Alla *Dott.ssa Picillo,* per essere stata una guida nell'acquisizione e nel consolidamento della gran parte delle conoscenze metodologiche e statistiche maturate in questi anni, per tutto il tempo dedicatomi nell'esercizio del ragionamento scientifico, per aver contribuito ad una più matura, autonoma e coraggiosa rappresentazione mentale di me stessa in ambito lavorativo.