A new MAPT deletion in a case of speech apraxia leading to corticobasal syndrome

Giulia Mazzon [a], Alina Menichelli[b], Antonella Fabretto[c], Tatiana Cattaruzza[a] and Paolo Manganotti[a]

[a]Neurological Clinic, Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy; [b]Neuropsychology Unit, Department of Rehabilitation Medicine, University of Trieste, Trieste, Italy; [c]Department of Advanced Diagnostic and Clinical Trials – Medical Genetics, Institute for Maternal and Child Health – IRCCS Burlo Garofolo, Trieste, Italy

ABSTRACT

Speech apraxia is a disorder of speech motor planning/programming leading to slow rate, articulatory distortion, and distorted sound substitutions. We describe the clinical profile evolution of a patient presenting with slowly progressive isolated speech apraxia that eventually led to the diagnosis of corticobasal syndrome (CBS), supporting the evidence that this rare speech disorder can be the first presentation of CBS. Moreover, we found a novel variant in MAPT gene, which is hypothesized to be disease-causing mutation. These results underscore the importance of genetic analysis – particularly in selected atypical cases – for *in vivo* understanding of possible pathophysiological disease process.

Accepted 18 June 2018

KEYWORDS

Speech apraxia; corticobasal syndrome; MAPT mutation; tauopathies; language disorders; parkinsonism

Introduction

Tauopathies are a group of neurodegenerative diseases characterized by deposits of misfolded, insoluble and hyperphosphorylated tau proteins in neuronal and glial cells. Their clinical spectrum is heterogeneous as they can present as frontotemporal dementia in all three variants (behavioral variant, semantic dementia, progressive nonfluent aphasia), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).

Tau protein is a microtubule-associated protein (MAP) encoded by the *MAPT* gene, whose main function is to promote microtubule assembly and stabilization, and to regulate their functioning (Gustke, Trinczek, Biernat, Mandelkow, & Mandelkow, 1994). It also contributes to nuclear function and genome stability (Morris, Maeda, Vossel, & Mucke, 2011; Rossi & Tagliavini, 2015).

Tauopathies are often sporadic, but genetic variants at the MAPT locus are a strong risk factor for the development of the disease, as they can interfere with tau functioning (i.e. tau splicing disruption, imbalance among the six tau isoforms with increased fibrillary aggregation, tau hyperphosphorylation with decrease in microtubule stability, etc.) (Dickson, Kouri, Murray, & Josephs, 2011; Spires-Jones, Stoothoff, De Calignon, Jones, & Hyman, 2009). Over than 50 mutations in MAPT gene have been so far described including deletions, insertions, base pair substitutions, missense and splice-site mutations (Rossi & Tagliavini, 2015). Most of these mutations have a dominant inheritance pattern with complete penetrance (Rossi et al., 2008).

The different ways to tau dysfunction justify phenotype variability of tauopathies; among all, CBS can present with typical features (progressive asymmetric bradykinesia, rigidity, dystonia, apraxia, alien limb phenomena, cortical sensory loss, and myoclonus), but possible manifestations include cognitive impairment, progressive nonfluent aphasia, speech apraxia, PSP-like syndrome and posterior cortical syndrome. Different pathological conditions are associated with CBS, including FTLD-tau, FTLD-TDP, dementia with Lewy bodies and Alzheimer disease (Boeve et al., 1999). In patients with familial and sporadic FTLD, mutations of MAPT, GRN, and C9orf72 genes are the most frequent (Galimberti & Scarpini, 2012).

We describe the clinical, neuropsychological and neuroimaging profile of a patient with isolated speech apraxia as presenting symptom of sporadic CBS, associated with a novel MAPT mutation.

Case presentation and results

A 74-year-old right-handed man was referred to our Ambulatory Clinic for Memory Disorders with a 1-year history of progressive isolated articulation impairment. His past medical history was unremarkable except for hypertension and a depressive episode when he was 37 years old. His family history was positive for depressive disorder; his parents died at 84 and 94 years, and his five siblings are still alive, with no history of motor, cognitive or behavioral problems. On first neurological examination, mild dysphonia and slow speech rate with articulatory impairment were found, with no fasciculations, sensory, pyramidal/extrapyramidal or cerebellar signs. Speech and language assessment (tested using the Motor Speech Evaluation – Duffy, 2005), Aachen Aphasia Test (Luzzatti, Willmes, & De Bleser, 1996), and Cookie Thief Test (Goodglass, Barresi, & Kaplan, 1983) revealed isolated apraxia of speech characterized by slow overall speech rate, mild dysphonia, abnormal prosody, distorted and inconsistent speech sound substitutions, segmentation of syllables in words productions with spared single-word comprehension, oral naming, and words repetition. Mild dysgraphia with letter substitutions and omissions was associated. Neuropsychological testing displayed mild slowness in scanning and visual search, and a dysexecutive syndrome with mild impairment in inhibition and planning, verbal working memory, and phonemic fluency.

Mini Mental Status Examination score, adjusted for age and education, was 30/30 (Table 1 – T1). Blood tests including complete blood count, liver and kidney function, glucose, thyroid hormones, vitamin B12, and folate were all within normal range. Brain magnetic resonance imaging (MRI) showed slightly asymmetric frontal, temporal and parietal cortical atrophy, right greater than left (Figure 1).

Two years later neurological examination revealed mild bradykinesia with bilateral impairment in rapid alternating movements, mild limb bilateral ideomotor apraxia (left worse than right), slowdown of right finger and foot tapping and saccade fragmentation without vertical gaze impairment; muscle tone and postural reflexes were normal. He was still independent in activities of daily living. His behavioral profile on the Neuropsychiatric Inventory was normal (except for mild depression reactive to speech impairment). He did not complain of dysautonomic symptoms or falls. Basal ganglia uptake was normal on Brain Single Photon Emission Tomography (SPECT) with DaTSCAN, while Brain Perfusion SPECT showed subtle hypoperfusion in the temporal pole and mesial temporal regions bilaterally (right greater than left). CSF analysis showed values within normal range: $A\beta_{42}$: 975 ng/L (normal values >550 ng/L) (Mulder et al., 2010), Tau 216 ng/L (normal values <375 ng/L) (Mulder et al., 2010), P-Tau: 38 ng/L (normal values <52 ng/L) (Mulder et al., 2010), and ratio $A\beta_{42}$/P-Tau: 25.7 (normal values >6–7) (Hansson et al., 2006). Neuropsychological testing revealed a worsening in speech apraxia, written production and visuospatial search speed, simplification of syntactic structure in oral production, mild deficit in oral comprehension of long and syntactic complex sentences. Errors in handwriting on dictation and in transcoding tasks from different

Table 1. Patient's scores on neuropsychological assessment performed at onset (T1) and 2 years later (T2).

			T1 (2013)	T2 (2015)
Tasks	Range	Cut offs	Raw score (adjusted score)	Raw score (adjusted score)
AAT-spontaneous speech: COM, ART, AUT, SEM, PHO, SYN	0–5		5 4 5 5 4 5	3 3 5 4 3 4
AAT-token test-*n*. of errors	0–50		**13**	**17**
AAT-repetition	0–150		**130**	**116**
AAT-written language:	0–90		**78**	**52**
Reading	0–30		29	**20**
Spelling with letter cards	0–30		**27**	**22**
Handwriting	0–30		**22**	**10**
AAT-oral naming on visual confrontation	0–120		111	114
AAT-comprehension:	0–120		**99**	**84**
Spoken-to visual matching	0–60		**49**	**43**
Written-to visual matching	0–60		**50**	**41**
Letter fluency (FAS)	–	≤17.35	**7 (15.6)**	**7 (16.4)**
Semantic fluency	–	≤24	40 (48)	32 (42)
Naming celebrities from faces	0–78	≤52.99	55 (55.2)	55 (56.17)
NPC-reading Arabic numbers	0–18	<17	19	19
NPC-writing Arabic numbers	0–18	<15	15	**14**
Digit Span fwd	0–9	<4.26	**3 (3.51)**	**3 (3.65)**
Digit Span bwd	0–8	<2.65	**2 (2.64)**	**2 (2.77)**
Corsi Span fwd	0–9	<3.46	5 (5.56)	4 (4.69)
Corsi Span bwd	0–8	<3.08	4 (4.31)	4 (4.5)
Prose memory: total recall	0–16	≤4.5	8.7 (9.2)	14.4 (15.15)
ROCF-delayed recall	0–36	≤9.46	6 (10.5)	n.a.
Warrington faces	0–25	–	23 (z = 0.43)	21 (z = −0.52)
TMT-A (s)	–	≥94	**124 (97)**	**202 (171)**
TMT-B (s)	–	≥283	**p.u.**	**p.u.**
FAB-frontal assessment battery	0–18	≤13.4	**8 (9.3)**	**9 (10.5)**
ToL-Tower of London	0–18.8	≤9.25	n.a.	16.06 (16.81)
Weight	0–15	≤4.5	9 (10)	9 (10.25)
Copy drawings	0–12	≤7.18	8 (9.2)	7 (8.3)
ROCF-copy	0–36	≤28.87	**24 (26.75)**	**p.u.**
Clock drawing test	0–10	≤5	3.5	6
Oro-buccal apraxia	0–20	≤16	18 (18)	**15 (15.25)**
Ideational apraxia: objects use	0–14	<14	14	14
Ideomotor apraxia: gestures imitation				
Total right arm	0–72	≤50	60	**42**
Meaningful right arm	0–36	≤25	30	**20**
Meaningless right arm	0–36	≤24	28	**22**
Total left arm	0–72	≤50	59	**35**
Meaningful gestures left arm	0–36	≤25	29	**18**
Meaningless gestures left arm	0–36	≤24	30	**17**

Notes: Data in boldface indicate performance outside the control range.

Abbreviations used in the neuropsychological assessment: AAT – Aachener Aphasie Test, Italian norms (Luzzatti et al., 1996), consists of five-point spontaneous speech rating scale (COM = communicative language, ART = articulation and prosody, AUT = automated language, SEM = semantic structure, PHO = phonological structure, SYN = syntactic structure); FAS – Letter Fluency; Semantic fluency (Carlesimo et al., 1996); Naming celebrities from faces presentation (Bizzozzero et al., 2007); NPC – Number Processing and Calculation battery (Delazer et al., 2003); Span fwd = digit span forward; Span bwd = digit span backward; Corsi test fwd (=forward) and bwd (=backward), spatial short-term memory and spatial working memory (Monaco et al., 2013); Prose Memory (Spinnler & Tognoni, 1987); Warrington Faces-Short Recognition Memory for Faces (Warrington, 1996); ROCF – Rey-Osterrieth Complex Figure test direct copy and delayed recall (Caffarra et al., 2002); TMT – Trail Making Test (Giovagnoli et al., 1996); FAB – Frontal Assessment Battery (Appollonio et al., 2005); ToL – Tower of London task (Franceschi et al., 2011); Weigl = Weigl's sorting test (Spinnler & Tognoni, 1987); Copy drawings (Carlesimo et al., 1996); Clock Drawing test (Mondini et al., 2003); Ideomotor apraxia: imitation of 18 meaningful intransitive gestures and 18 meaningless intransitive gestures (Tessari et al., 2011); Ideational apraxia: seven objects use (De Renzi et al., 1988); Oro-buccal gestures (Spinnler & Tognoni, 1987); n.a. – task not administered; p.u. – patient unable to perform the task.

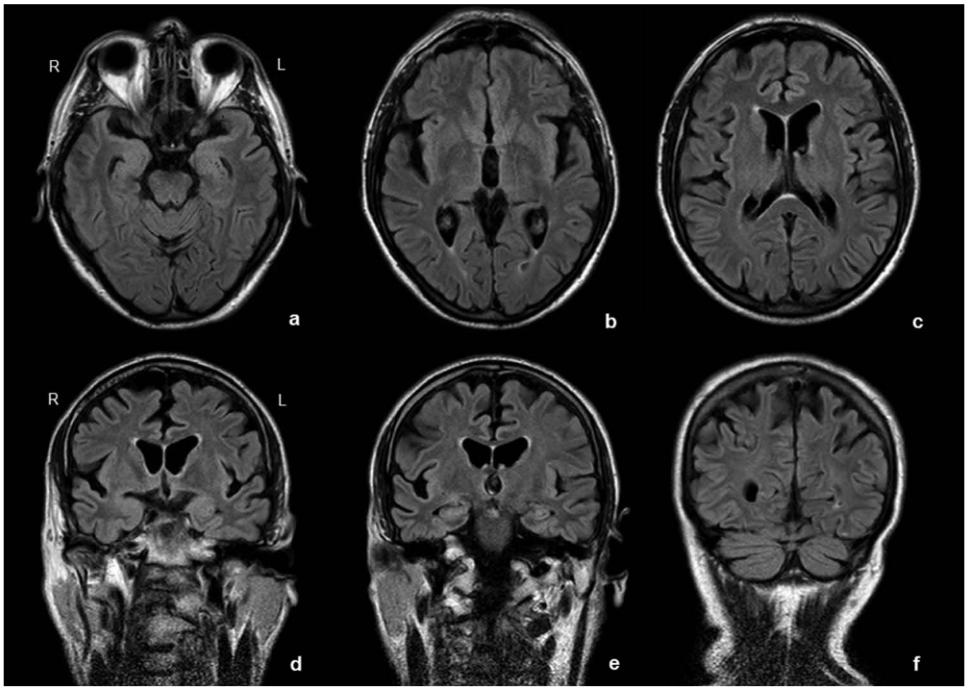

Figure 1. Brain magnetic resonance imaging (MRI), axial (a–c) and coronal (d–f) FLAIR sequence: showed right greater than left cortical atrophy in frontal, temporal and parietal regions. R = right, L = left.

case/style consisted of incomplete and poorly formed letters, letter substitutions and omissions. Copy was much more preserved, especially in upper print case. In fact, agraphic disturbances were much more severe for lower-case cursive than for upper-case print. Moreover, a difficulty to maintain writing within lower-case cursive was observed in handwriting to dictation and in transcoding from upper-case print to lower-case cursive (mixed-case errors), but not in direct copy. Spelling with mobile letters was much preserved than handwriting, although patient made some letter omissions and substitutions. It seems that an impairment occurs at the level of graphic pattern store leading to an inability to retrieve the correct letter motor patterns (apraxic agraphia); in addiction a more central deficit could not be ruled out. Finally, ideomotor, buccofacial and constructional apraxia emerged. Phonological and verbal working memory tasks were still defective, episodic memory for verbal and visual material was spared (Table 1 – T2).

Due to the suspicion of an underlying FTLD pathology, genetic counseling was required. *PGRN* and *C9ORF72* sequencing did not reveal any mutation, but we found a 15bp deletion (c.105–119del,p.Gln35_Asp40delinsHis) in *MAPT* gene, not yet described in the literature. Prediction software such as Mutation Taster® and Polyphen® suggest that this is a possible disease-causing mutation, as the long deletion can affect normal protein transcription, thus altering its stability or function. Searching for this variant in healthy human mutation database as ExAC and 1000G gave negative results.

At 4 years from symptom onset, neurological examination shows almost stable speech apraxia associated with some comprehension difficulties, mild bradykinesia with preserved postural reflexes; bilateral postural tremor, mild impairment in finger tapping, and rapid alternating movements (left worse than right), mild symmetric plastic increased tone, worsening of ideomotor apraxia with exclusively body-part-as-a-tool errors when pantomiming object use. Saccade fragmentation without vertical gaze impairment and mild dysphonia are unchanged. Dysphagia is absent, as well as falls, cortical sensory deficits, behavioral and dysautonomic symptoms. A final diagnosis of speech apraxia leading to CBS was made.

Discussion

We described a case of isolated speech apraxia as symptom onset of possible CBS, associated with a novel MAPT mutation.

According to the recent consensus diagnostic criteria, the clinical diagnosis of probable CBS requires at least two asymmetric motor symptoms (rigidity, akinesia, dystonia, and myoclonus) plus at least two non-motor symptoms (oro-buccal or limb apraxia, agnosia, cortical sensory loss, or alien limb phenomena); for possible, CBS one motor and one non-motor symptoms are needed (Armstrong et al., 2013; Alexander et al., 2014). Apraxia of speech is a disorder of speech motor planning or programming leading to slow rate, articulatory distortion, and distorted sound substitutions. It can be isolated (Primary Progressive Apraxia of Speech – PPAOS) or can be a component of a degenerative syndrome (Josephs et al., 2012) as PSP (Josephs et al., 2014) or CBS (Assal, Laganaro, Remund, & Ragno Paquier, 2012; Josephs & Duffy, 2008). Speech apraxia belongs to the Nonfluent/Agrammatic variant of primary progressive aphasia (nfvPPA) phenotype of CBS, associated with corticobasal degeneration (CBD) pathology (Armstrong et al., 2013).

Our patient presented with isolated speech apraxia with final evolution into possible CBS, characterized by asymmetric mild akinesia with oro-buccal and ideomotor limb apraxia. All the exclusion criteria (Armstrong et al., 2013) have been ruled out, as there is no evidence of Lewy Body disease, multiple system atrophy, amyotrophic lateral sclerosis, primary progressive aphasia,

structural focal lesions, or Alzheimer's disease. Both structural and functional neuroimaging were not specific, as they revealed only slightly asymmetric fronto-temporo-parietal atrophy and temporal hypoperfusion, respectively.

Recently, some authors stated that in patients with nfvPPA, an early severe dysarthria, a relative selective white matter atrophy and a greater rate of change in the brainstem are predictive of more prominent behavioral symptoms, and brain atrophy involving white matter and left frontal gray matter, are suggestive of CBD pathology (Santos-Santos et al., 2016). Our patient did not have any predictive features of underlying CBD on presentation, as he had only gray matter atrophy on MRI, no sentence comprehension deficits, nor behavioral symptoms at 3 years from presentation. Moreover, he had some slowness in scanning and visual search at first evaluation, which could be supportive of PSP. All subjects with PPAOS develop extrapyramidal signs in the evolution of the disease, in some of them apraxia of speech remains the predominant feature, in the others the progression of symptoms evolves most commonly into a PSP-like syndrome (Josephs et al., 2014). In our patient the progression of symptoms began after 3 years of isolated apraxia of speech and, although mild PSP-like features are present, a CBS phenotype appears predominant.

Mutations in the three genes usually associated with FTD (MAPT, GRN, C9ORF72) seems to be not commonly associated with PPAOS as show by Flanagan et al. where no mutations were detected in any of the 40 patients with PAOS (Flanagan et al., 2015); just one case of PAOS with a P332S MAPT mutation has been reported (Deramecourt et al., 2012). Few cases of CBS associated with MAPT mutation have so far been described (Kouri et al., 2014); among them, only one patient had speech apraxia as first symptom (the mutation found was NM 005910.5:c.871T>C, p.[Cys291Arg]) (Marshall et al., 2015). Compared to the case report by Marshall et al., our patient did not present with limb apraxia till 3 years from symptom onset, he does not have any pyramidal involvement and his family history is completely negative, suggesting a probable sporadic mutation.

The pathogenicity of this novel mutation has still to be confirmed, but current prediction sites, its nature and extent (long deletion), as well as its absence in a healthy subjects' database, point to a probable causative effect.

To our knowledge, Tau mutations involved in frontotemporal lobar degeneration, as well as the mutation described by Marshall et al., map primarily to exons 9–12 or to the intronic region between exons 10 and 11; these intronic mutations increase the prevalence of exon 10-containing 4R tau. The novelty of the mutation here described is related to its nature (long deletion) and position on MAPT gene (exon 2). As it was not possible to analyze the DNA of proband's parents and neuropathological study is still not available, an *in vitro* structural and biochemical characterization is in progress and will increase our knowledge into the pathogenicity of this mutation. We hypothesize that this sporadic mutation could change our clinical diagnosis in isolated speech apraxia leading to possible CBD (Armstrong et al., 2013).

Acknowledgments

The authors thank Dr. Urôs Hladnik and the B.I.R.D. Foundation Laboratory in Costozza di Longare for the genetic analysis of *PGRN, C9ORF72, MAPT* genes and the MAPT mutation analysis.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Giulia Mazzon http://orcid.org/0000-0003-0382-5975

References

Alexander, S. K., Rittman, T., Xuereb, J. H., Bak, T. H., Hodges, J. R., & Rowe, J. B. (2014). Validation of the new consensus criteria for the diagnosis of corticobasal degeneration. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*, 925–929.

Appollonio, I, Leone, M, Isella, V, Piamarta, F, Consoli, T, Villa, M. L, & Nichelli, P. (2005). The frontal assessment battery (fab): normative values in an italian population sample. *Neurological Sciences*, *26*(2), 108-116.

Armstrong, M. J., Litvan, I., Lang, A. E., Bak, T. H., Bhatia, K. P., Borroni, B., … Weiner, W. J. (2013). Criteria for the diagnosis of corticobasal degeneration. *Neurology*, *80*, 496–503.

Assal, F., Laganaro, M., Remund, C. D., & Ragno Paquier, C. (2012). Progressive crossed-apraxia of speech as a first manifestation of a probable corticobasal degeneration. *Behavioural Neurology*, *25*, 285–289.

Bizzozero, I, Lucchelli, F, Saetti, M. C, & Spinnler, H. (2007). "whose face is this?": italian norms of naming celebrities. *Neurological Sciences*, *28*(6), 315-322. doi:10.1007/s10072-007-0845-6

Boeve, B. F., Maraganore, D. M., Parisi, J. E., Ahlskog, J. E., Graff-Radford, N., Caselli, R. J., … Petersen, R. C. (1999). Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. *Neurology*, *53*, 795–800.

Caffarra, P, Vezzadini, G, Dieci, F, Zonato, F, & Venneri, A. (2002). Rey-osterrieth complex figure: normative values in an italian population sample. *Neurol Sci*, *22*(6), 443-447. doi:10.1007/s100720200003

Carlesimo, G. A, Caltagirone, C, Gainotti, G, Fadda, L, Gallassi, R, Lorusso, S, & Parnetti, L. (1996). The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. *European Neurology*, *36*(6), 378-384.

De Renzi, E, & Lucchelli, F. (1988). Ideational apraxia. *Brain*, *111*(5), 1173-1185. doi:10.1093/brain/111.5.1173

Delazer, M, Girelli, L, Gran, A, & Domahs, F. (2003). Number processing and calculation ? normative data from healthy adults. *The Clinical Neuropsychologist*, *17*(3), 331-350. doi:10.1076/clin.17.3.331.18092

Deramecourt, V., Lebert, F., Maurage, C. A., Fernandez-Gomez, F. J., Dujardin, S., Colin, M., … Buee, L. (2012). Clinical, neuropathological, and biochemical characterization of the novel tau mutation P332S. *Journal of Alzheimer's Disease: JAD*, *31*, 741–749.

Dickson, D. W., Kouri, N., Murray, M. E., & Josephs, K. A. (2011). Neuropathology of frontotemporal lobar degeneration-tau (FTLD-tau). *Journal of Molecular Neuroscience: MN*, *45*, 384–389.

Duffy, J. R. (2005). Motor speech disorders: Substrates, differential diagnosis, and management 2nd edition (St Louis, MO: Mosby). *Google Scholar*.

Flanagan, E. P., Baker, M. C., Perkerson, R. B., Duffy, J. R., Strand, E. A., Whitwell, J. L., … Josephs, K. A. (2015). Dominant frontotemporal dementia mutations in 140 cases of primary progressive aphasia and speech apraxia. *Dementia and Geriatric Cognitive Disorders*, *39*, 281–286.

Franceschi, M., Caffarra, P., Savare, R., Cerutti, R., & Grossi, E. (2011). Tower of London test: a comparison between conventional statistic approach and modelling based on artificial neural network in differentiating fronto-temporal dementia from Alzheimer's disease. *Behav Neurol*, *24*(2), 149–158.

Galimberti, D., & Scarpini, E. (2012). Clinical phenotypes and genetic biomarkers of FTLD. *Journal Neural Transm (Vienna)*, *119*, 851–860.

Giovagnoli, A. R, Del Pesce, M, Mascheroni, S, Simoncelli, M, Laiacona, M, & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *Ital J Neurol Sci*, *17*(4), 305-309. doi:10.1007/BF01997792

Goodglass, H, & Kaplan, E. (1983). *Boston diagnostic examination for aphasia*. Philadelphia: Lea & Febiger.

Gustke, N., Trinczek, B., Biernat, J., Mandelkow, E. M., & Mandelkow, E. (1994). Domains of tau protein and interactions with microtubules. *Biochemistry*, *33*, 9511–9522.

Hansson, O., Zetterberg, H., Buchhave, P., Londos, E., Blennow, K., & Minthon, L. (2006). Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: A follow-up study. *Lancet Neurology*, *5*, 228–234.

Josephs, K. A., & Duffy, J. R. (2008). Apraxia of speech and nonfluent aphasia: A new clinical marker for corticobasal degeneration and progressive supranuclear palsy. *Current Opinion in Neurology*, *21*, 688–692.

Josephs, K. A., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Gunter, J. L., … Whitwell, J. L. (2014). The evolution of primary progressive apraxia of speech. *Brain: A Journal of Neurology*, *137*, 2783–2795.

Josephs, K. A., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Master, A. V., … Whitwell, J. L. (2012). Characterizing a neurodegenerative syndrome: Primary progressive apraxia of speech. *Brain: A Journal of Neurology*, *135*, 1522–1536.

Kouri, N., Carlomagno, Y., Baker, M., Liesinger, A. M., Caselli, R. J., Wszolek, Z. K., … Rademakers, R. (2014). Novel mutation in MAPT exon 13 (p. N410H) causes corticobasal degeneration. *Acta Neuropathologica*, *127*, 271–282.

Luzzatti, C., Willmes, K., & De Bleser, R. (1996).Aachener aphasie test: versione italiana. Giunti Organizzazioni Speciali. Firenze.

Marshall, C. R., Guerreiro, R., Thust, S., Fletcher, P., Rohrer, J. D., & Fox, N. C. (2015). A novel MAPT mutation causing corticobasal syndrome led by progressive apraxia of speech. *Journal of Alzheimer's Disease: JAD*, *48*, 923–926.

Monaco, M, Costa, A, Caltagirone, C, & Carlesimo, G. A. (2013). Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an italian adult population. *Neurol Sci*, *34*(5), 749-754. doi:10.1007/s10072-012-1130-x

Mondini, S., Mapelli, D., Vestri, A., & Bisiacchi, P. S. (2003). Esame neuropsicologico breve. *Milano: Raffaello Cortina Editore*, *160*.

Morris, M., Maeda, S., Vossel, K., & Mucke, L. (2011). The many faces of tau. *Neuron*, *70*, 410–426.

Mulder, C., Verwey, N. A., Van Der Flier, W. M., Bouwman, F. H., Kok, A., Van Elk, E. J., … Blankenstein, M. A. (2010). Amyloid-beta(1–42), total tau, and phosphorylated tau as cerebrospinal fluid biomarkers for the diagnosis of Alzheimer disease. *Clinical Chemistry*, *56*, 248–253.

Rossi, G., Marelli, C., Farina, L., Laura, M., Maria Basile, A., Ciano, C., … Pareyson, D. (2008). The G389R mutation in the MAPT gene presenting as sporadic corticobasal syndrome. *Movement Disorders: Official Journal of the Movement Disorder Society*, *23*, 892–895.

Rossi, G., & Tagliavini, F. (2015). Frontotemporal lobar degeneration: Old knowledge and new insight into the pathogenetic mechanisms of tau mutations. *Frontiers in Aging Neuroscience*, *7*, 192.

Santos-Santos, M. A., Mandelli, M. L., Binney, R. J., Ogar, J., Wilson, S. M., Henry, M. L., … Rosenberg, L. (2016). Features of patients with nonfluent/agrammatic primary progressive aphasia with underlying progressive supranuclear palsy pathology or corticobasal degeneration. *JAMA Neurology*, *73*, 733–742.

Spinnler, H, & Tognoni, G. (1987). *Standardizzazione e taratura italiana di test neuropsicologici*. Masson Italia Periodici.

Spires-Jones, T. L., Stoothoff, W. H., De Calignon, A., Jones, P. B., & Hyman, B. T. (2009). Tau pathophysiology in neurodegeneration: A tangled issue. *Trends in Neurosciences*, *32*, 150–159.

Tessari, A., Toraldo, A., Lunardelli, A., Zadini, A., & Rumiati, R. I. (2011). Prova standardizzata per la diagnosi del disturbo aprassico ideomotorio selettivo per tipo di gesto e tipo di effettore. *Ricerche di Psicologia*.

Warrington, E. K. (1996). Short Recognition Memory Test for Faces: Psychology Press.